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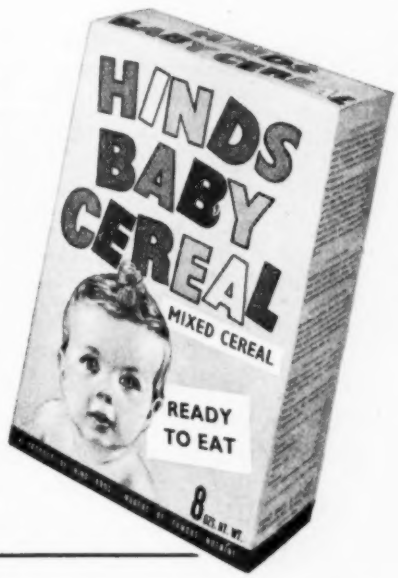


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# CLINICAL EXPERIENCE WITH A NEW ULTRA-SHORT-ACTING THIOBARBITURATE

H. GRANT-WHYTE, F.F.A.R.C.S. (ENG.), D.A.

*Durban*

Barbital was prepared by Fischer and von Meiring in 1905, and phenobarbital by Horlein in 1911; and in 1916 Schonle began to prepare the higher-molecular-weight derivatives. In 1930 Nembutal marked the beginning of the use of intravenous barbiturates, and Evipan sodium followed in 1932. In 1934 Sodium pentothal (thiopentone) was introduced by Lundy and Tovell at the Mayo Clinic.

It was stated by A. J. Clark in 1937 that the number of possible barbiturate homologues, none containing more than 6 carbon atoms in a side-chain, was in the neighbourhood of 1,225; today 100 have been prepared and used.

In anaesthesia, barbituric acid and its salts and derivatives are generically known as barbiturates. The most useful of them have been the ultra-short-acting group, which are characterized by rapidity of induction and pronounced intense hypnotic action of brief duration, followed by mild hypnosis or heavy sedation. This group have been useful for abolition of consciousness during surgical procedures. The barbiturates in this group are in the main 'thio' or sulphur containing; they are described as ultra-short-acting because of their rapid disappearance in the body. Detoxification takes place by the action of the liver, muscle tissue and the blood, possibly through enzyme action.

Constant search for new and innocuous ultra-short-acting barbiturates has resulted in the synthesis of a new thiobarbiturate—the sodium salt of methyl-thio-ethyl 2 pentyl-thiobarbituric acid, Neraval sodium (Sch. 3132), also known as Thiogenal. This drug is of particular interest because of the presence of the methyl-thio-ethyl radicle, which is present in methionine—an essential amino acid which has itself a detoxifying action.

## SERIES OF CASES REPORTED

Neraval sodium has been used in 80 unselected cases by intermittent intravenous injection of aqueous solution of 5% concentration; all cases except dental extractions were supplemented with nitrous oxide and oxygen mixture 50 : 50. Muscle relaxants, long-acting or short-acting, were used when surgical procedures demanded their use. Pre-anaesthetic medication with Omnopon, 1/6th to 1/3rd gr., and scopolamine, 1/300th to 1/150th gr., was administered 1½ hours before operation, except for dental extractions, when no preliminary narcotic was administered because they were carried out in dental chambers.

The table below shows an analysis of cases by type of surgery, age range, and dosage of Neraval sodium 5% and of long-acting relaxant (Laudolissin- Laudexin) and/or short-acting succinylcholine chloride (Scoline) when these were employed.

Neraval sodium is a crystalline substance, yellowish in colour and dissolving slowly in distilled water, forming a solution which has a sulphurous odour. A 2·5% solution has a pH of 9·42, a 5% solution 9·32 (2·5% Sodium pentothal has a pH of 10·5). Deterioration of solutions is said to occur in much the same way as with solutions of other thiobarbiturates, although 40 c.c. of a 5% solution of Neraval sodium was kept 2 days in a refrigerator and exhibited no loss of potency when used subsequently.

## DOSAGE AND ADMINISTRATION OF NERAVAL SODIUM 5%

The average human dose for the induction of sleep is in the region of 0·01 g. per kg. of body-weight, and the same precautions were taken with this drug as with other barbiturates.

A slow rate of intravenous administration is advisable, and was in fact practised because it was found in the first few cases that too rapid injection resulted in coughing due to laryngeal irritation. The practice subsequently was to administer 1 c.c. as a test dose and subsequently fractional doses of 3 c.c. Sleep was induced with 6-15 c.c. of 5% solution.

Larger repeat doses had to be administered than

EIGHTY SURGICAL PROCEDURES UNDER NERAVAL NARCOSIS

| Type of Surgery | No. of Cases | Age Range (Years) | Average Dose of Neraval Sodium 5% (g.) | Relaxant Drug |
|---|---|---|---|---|
| 1. *Dental Extractions* | 6 | 15-18 | 0·5-1·5 | |
| 2. *Gynaecological* | 18 | 28-50 | 1·0-2·0 | Laudolissin 30-60 mg. Nil |
| Ventrosuspension and operations on adnexa<br>Insertion of radium<br>Dilation of cervix<br>Dilation of vagina<br>Vaginal hysterectomy<br>Opening pelvic abscess | | | | |
| 3. *Urological* | 17 | 30-84 | 1·5-3·5 | Laudolissin 30-60 mg. |
| Cystoscopy<br>Suprapubic cystotomy<br>Suprapubic prostatectomy<br>Retrograde pyelogram<br>with extensive cystodiathermy<br>Urethral dilation | | | | |
| 4. *General Surgery* | 29 | 18-60 | 1·5-3·5 | With and without Laudolissin 30-60 mg. or Scoline 70-100 mg. |
| Appendectomy<br>Herniorrhaphies, direct, indirect, post-operative and ventral<br>Tumours of breast, simple and malignant<br>Mobilization of colostomy and closure<br>Sigmoidoscopy<br>Haemorrhoidectomy | | | | |
| 5. *Orthopaedic* | 6 | 24-55 | 1·0-1·5 | Scoline 70-100 mg. |
| 6. *Thoracic* | 4 | 28-35 | 1·5-2·0 | Laudolissin 30-60 mg. |

would have been the case if Sodium pentothal had been used, and there was no difference between the two drugs as far as the production of hypotension was concerned, the fall of blood pressure being more pronounced in hypertensive patients than in normotensive.

Extravenous injection of Neraval sodium in 2 cases in the series produced the usual discomfort experienced with Sodium pentothal, but the clinical impression was that Neraval sodium was less irritating to the endothelium of the veins, and led to less 'hardening' of the vein post-operatively. The reason for this is possibly the lower pH of Neraval sodium, resulting in less irritation of the endothelium and less tendency for the vein to thrombose.

Poor-risk octogenarians tolerated the drug extremely well. One of these oldsters received 3·5 g. of Neraval sodium over a period of 2½ hours and was awake within 15 minutes of leaving the operating theatre.

Laryngospasm was almost negligible in the series of cases. There was slight evidence of it in a few cases where the drug was administered with injudicious rapidity, but even in these there was no indication to use relaxant to alleviate the spasm.

SUMMARY

1. A brief clinical report is submitted on the use of Neraval sodium (Sch. 3132) in 80 unselected cases embracing a wide range of surgery.

2. Dosage and administration of Neraval sodium is discussed.

3. Beyond slight laryngospasm in 3 cases, and slight vein reaction in 2 other cases, there were no other untoward effects in the nature of severe respiratory depression or severe hypotension resulting from accumulation of the drug.

4. 'Waking up' time is markedly shorter than with other barbiturates, which is of great advantage to the patient, nursing staff and surgeon.

5. In conclusion, Neraval sodium has a definite use for brief surgical procedures; its use is free from unpleasant after-effects; and its outstanding quality is that it allows of rapid awakening after small or large doses.

I would like to express my thanks to the Schering Corporation, Bloomfield, New Jersey, USA, for supplying me with Neraval sodium for clinical trial.

## QUESTIONS ANSWERED

1. Hoe kom spermatazoa van die testes in die seminêre vesikels. 2. Hoe lank leef hierdie sperme in die buisie. 3. As 'n man gesteriliseer word deur vaso-afbinding, vir hoe 'n lang periode sal hy nog vrugbaar wees as gevolg van die saad in die vesikels. 4. Is dit moontlik dat die vas weer kan rekondiseer na dit afgebind en tussen die afbinding deurgesny is?

1. Die ampul van die buis ontmoet die aansluiting van die saadblase en die uitstortingsbuise met 'n skerp hoek. Die spermatazoa vind hulle weg agterwaarts na die saadblase. Die juiste meganisme hiervan is onbekend.

2. Ongeveer 3 maande.

3. Die pasiënt is waarskynlik binne 'n paar weke steriel, maar dit is nie raadsaam om hierop, sonder 'n spermtelling, te reken nie.

4. Ná vasektomie is dit heel moontlik dat omtrent 'n helfte van die gevalle deur operasie herstel kan word. Spontane herstelling is hoogs onwaarskynlik.

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## EDITORIAL

### ABOUT OBESITY

Obesity, like smoking, affects so many scientific and medical men personally that there is some difficulty in viewing the subject dispassionately. First of all it should be recognized as a serious disease. Jean Mayer, whose review of the Etiology of Obesity is the inspiration for this article, considers it to be perhaps the 'Number-One Public-Health Problem' in Western countries at the present time. Secondly it should be realized that man has no immunity from the workings of the Second Law of Thermodynamics. If he takes in more calories than he needs, he will gain weight; as Mayer says, 'in the development of 100 per cent of the cases of obesity, there must be excess intake'. There are no known exceptions. It is really remarkable how accurately the mechanism of appetite does control the constancy of weight in a large number of people.

Mayer considers in some detail what these mechanisms are that control the appetite. It seems beyond doubt that there is an 'appetite' centre in the hypothalamus. Destruction of parts of the ventro-median nuclei leads to obesity, while more lateral lesions cause anorexia. Over the last several years Mayer and his associates have elaborated the 'glucostatic' theory of regulation of food intake. They argued that the central nervous system, which is known to be dependent upon a continued supply of glucose in the blood, might maintain 'glucoreceptors' which are sensitive to fluctuation in available blood glucose. Hunger thus becomes one of the mechanisms by which the central nervous system ensures its own homeostasis.

Injection of glucose, fructose and epinephrine caused temporary raising of blood glucose and lowered the food intake correspondingly. Injections of sucrose and fat emulsion were without effect. More remarkable was the effect of injections of glucose upon alloxan-diabetic hypophysectomized rats. These animals were deprived of their mechanisms for recovery from hyperglycaemia. Three daily injections of glucose, maintaining continuous hyperglycaemia, caused death of the animals from inanition in spite of the presence of food in the cage.

Mayer and his associates reasoned further that the

## VAN DIE REDAKSIE

### OOR VETSUG

Vetsug, net soos die rookgewoonte, raak so baie van ons wetenskaplikes en medici persoonlik, dat dit ietwat moeilik sal gaan om hierdie onderwerp onpersoonlik te bespreek. Eerstens moet dit as 'n gevaarlike siekte beskou word. Jean Mayer, wie se hersiening van die *Etiology of Obesity* hierdie artikel geïnspireer het, beskou dit as die ‚Number-One Public-Health Problem' in die Westerse lande vandag. Tweedens moet ons besef dat die mens geen immuniteit teen die werking van die Tweede Wet van Termodinamika het nie. As hy meer kalorieë opneem as wat hy nodig het, sal hy gewig optel; soos Mayer sê, ‚in the development of 100 per cent of the cases of obesity, there must be excess intake'. Geen uitsondering is bekend nie. Dit is werklik opvallend hoe akkuraat die aptytmeganisme die gewigskonstantheid in 'n groot aantal mense beheer.

Mayer oorweeg taamlik breedvoerig die meganisme wat die aptyt reël. Dit ly geen twyfel dat daar 'n ‚aptyt'-sentrum in die hipotalamus is nie. Vernietiging van dele van die ventromediaankern lei tot vetsug, terwyl meer laterale letsels aptytverlies veroorsaak. Gedurende die afgelope paar jaar het Mayer en sy medewerkers die ‚*glucostatic*'-teorie van die voedselopname-reëling verwerk. Hulle het geredeneer dat die sentrale senuweestelsel—bekend vir sy afhanklikheid van 'n onafgebroke toevoer van glukose in die bloed—miskien ‚*glucoreceptors*' in stand hou, wat sensitief is vir skommelinge in die beskikbare bloedglukose. Honger word dus 'n meganisme waardeur die sentrale senuweestelsel sy eie ewewig behou.

Inspuitings van glukose, vrugtesuiker en epinefrien het 'n tydelike verhoging van die bloedglukose en 'n dienooreenkomstige verlaging van die voedselopname veroorsaak. Inspuitings van sukrose en vet-emulsie het geen effek gehad nie. Nog merkwaardiger was die uitwerking van glukose-inspuitings op alloksaandiabetiese rotte wie se hipofise verwyder was. In hierdie diere was die meganisme vir die herstel van hiperglisemie ontneem. Drie daaglikse inspuitings van glukose, wat sonder onderbreking die hiperglisemie volgehou het, het daartoe gelei dat die diere as gevolg van uitputting gevrek het, ten spyte daarvan dat daar kos in die hok was.

Mayer en sy medewerkers het verder geredeneer dat die aptytsentrum in die brein nie sensitief was nie vir die werklike bloedglukose-hoogte nie, maar eerder vir die beskikbaarheid van die bloedglukose—dit moet eers oor membrane gaan om die gluko-ontvangerselle binne te dring, en dit veronderstel integriteit van fos-

appetite centre in the brain was not sensitive to the actual level of blood glucose, but rather to its availability—it first must cross membranes to enter the glucoreceptor cells, and this implies the integrity of phosphorylation. Hence in diabetes mellitus the sufferer may be hyperphagic despite a high blood-glucose level. To test this theory one would like to estimate the utilization of glucose in the hypothalamus itself. Since this is impossible in man, measurements of arteriovenous glucose differences (called '$\lambda$ glucose') were adopted as indices of glucose utilization.

Large numbers of experiments on man confirmed the postulated alterations of $\lambda$ glucose varying inversely with appetite. The relationship was found to hold normally, on subnormal diets, in diabetes and hyperthyroidism, after cortisone administration, and after insulin. It was also applied to various types of experimental obesity.

This scheme of glucostatic control of appetite is simple and attractive, but it must be pointed out that it is by no means proved and it has not everywhere found favour. In any event it is plain that the physiological mechanism of regulation of food intake is exceedingly complicated and correspondingly vulnerable.

Conditions which increase appetite without corresponding increase in energy expenditure are therefore those which lead to obesity. The first factor to be considered is the genetic one. Obesity due to a dominant gene occurs in a yellow strain of mice. The proximate cause of their obesity is unknown, though they favour a high food-intake and low level of activity. Another genetic obesity in mice is the 'hereditary obese-hyperglycaemia syndrome', controlled by an autosomal recessive gene. These enormously obese animals show no increase in oxygen consumption over non-obese controls. Unlike the state of affairs in human obesity, where subjects have 'normal' basal metabolism, the basal metabolic rate of these mice, referred in the usual way to surface area, may be less than 50%. Their food intake is only some 25% greater than that of the non-obese litter-mates, but they are 50 to 100 times less active. Their calorie intake, then, although little above normal, is still enormously greater than their metabolic need.

These obese mice are interesting also for another reason—they develop progressively severe hyperglycaemia and glycosuria. Strangely enough, high-fat diets tend to cause loss of weight, while high-protein diets increase weight and increase the severity of the diabetes. From a variety of evidence, Mayer and his associates have suggested that the obese animals secrete an excess of glucagon from overactivity of the alpha cells of their pancreatic islets. This would account for their hyperglycaemia and insulin-resistance. The basic biochemical lesion is said to be a slowing down of the process of oxidation of acetate to carbon dioxide and water.

Interesting as these mice undoubtedly are, with their superficial resemblance to human obese diabetics, it must be doubtful whether there is any basic analogy.

Mayer, J. (1953): Physiol. Rev., **33**, 472.

forilering. Dus is dit moontlik dat 'n suikersiektepasiënt aan verhoogde-voedselopname kan ly ten spyte daarvan dat sy bloedglukose hoog is. Om hierdie teorie te toets, sou 'n mens graag die gebruikmaking van glukose in die hipotalamus sigself wou skat. Aangesien dit by die mens onmoontlik is, is die meet van arterioveneusglukose-verskille (genoem ‚$\lambda$ glukose') as indeks van glukosegebruikmaking aanvaar. Die gepostuleerde veranderings van $\lambda$ glukose met omgekeerde veranderings van aptyt is deur baie eksperimente op die mens bevestig. In gevalle van suikersiekte en oormatige skildklierwerking is gevind dat—met subnormale dieëte—die verhouding normaal bly ná toediening van kortisoon en insuline. Dit was ook by verskeie tipes van eksperimentele vetsug gebruik.

Hierdie plan vir glukostatiese beheer van aptyt is eenvoudig en aantreklik, maar daar moet op gelet word dat dit nog glad nie bewys is nie, en dat dit nie orals byval gevind het nie. Dit is in elk geval baie duidelik dat die fisiologiese meganisme van voedselopname-reëling baie ingewikkeld is en dienooreenkomstig vir kritiek vatbaar is. Toestande wat die aptyt verhoog sonder om die energieverbruik ooreenkomstig te verhoog, lei tot vetsug. Die erflikheidsfaktor is die eerste wat oorweeg word. Vetsug te wyte aan 'n dominante geen kom in 'n geel ras van muise voor. Die onmiddellike oorsaak van hulle vetsug is onbekend, alhoewel hulle geneig is tot 'n hoë voedselopname en 'n lae peil van aktiwiteit. 'n Ander tipe erflike vetsug in muise is die *‚hereditary obese-hyperglycaemia syndrome*', wat deur 'n resessiewe outosoom-geen beheer word. Hierdie enorme vetsugtige diere toon geen verhoging van suurstofverbruik in vergelyking met nie-vetsugtige kontrolediere nie. Anders as in die geval van menslike vetsug waar die pasiënte se basale metabolisme normaal is, kan die basale metaboliese koers van hierdie muise, soos gebruiklik verwys na oppervlaktegebied, minder as 50% wees. Hulle voedselopname is slegs sowat 25% groter as dié van hul werpselmaats wat nie aan vetsug ly nie, maar hulle is sowat 50-100 maal minder aktief. Hulle kalorieopname derhalwe, alhoewel bietjie bo normaal, is nogtans geweldig groter as hul metaboliese vereiste.

Ook om 'n ander rede is hierdie vetsugtige muise interessant—progressief ontwikkel hul swaar hiperglisemie en glikosurie. Eienaardig genoeg is dieëte ryk aan vet geneig om gewigsverlies te veroorsaak, terwyl dieëte nut hoë proteiengehalte die gewig vermeerder en die hewigheid van die diabetes laat toeneem. 'n Verskeidenheid van bewyse het Mayer en sy medewerkers op die gedagte gebring dat die vetsugtige diere 'n oormaat van glukagon afskei as gevolg van ooraktiwiteit van die alfaselle van hul alvleesklier-eilandjies. Dit sal hul hiperglisemie en insuline-weerstand verklaar. Dit word beweer dat die basiese biochemiese letsel 'n vertraging van die oksidering van asetaat na koolsuurgas en water is.

So interessant soos hierdie muise met hulle oppervlakkige ooreenkoms met vetsugtige suikersiektepasiënte ongetwyfeld is, moet dit betwyfel word of enige basiese analogie bestaan.

Mayer, J. (1953): Physiol. Rev. **33**, 472.

## NOVOBIOCIN

Much interest has been aroused by the new antibiotic, novobiocin, largely on account of its activity against staphylococci and other organisms which are or have become resistant to the commonly-used antibiotics, and also because of the high concentrations of novobiocin in the blood that have been achieved. Active research is still proceeding. An interesting line is the investigation of the apparent identity or relationship of some antibiotics obtained from different organisms.

Novobiocin is well known under its trade names of Albamycin (Upjohn Co.), Cathomycin (Merck) and Cardelmycin (Pfizer).

*In vitro*[1] studies of novobiocin indicate especially high activity against *Staphylococcus aureus* and effectiveness against *Streptococcus haemolyticus*, *Streptococcus viridans* and *Diplococcus pneumoniae*, as well as several other gram-positive organisms. Of the gram-negative organisms, the most susceptible have been found to be *Proteus vulgaris*, *Pasteurella multocida* and *Klebsiella pneumoniae*. The drug was similarly highly effective against induced infections *in vivo* with these organisms. Lubach[2] tested 182 strains of *Staphylococcus aureus* and only one strain failed to be inhibited by 1·0 μg./ml. of novobiocin. The majority of the tested strains were inhibited by considerably lower concentrations of the drug and were highly resistant to the commonly used antibiotics.

Novobiocin is bactericidal rather than bacteriostatic.[3] No cross-resistance with any other antibiotics was observed.[4] While resistance may develop *in vitro*, it usually occurs in a stepwise, penicillin-like manner instead of the rapidly increasing type noted for streptomycin.

When a therapeutic dose of novobiocin is administered orally to dogs or man, absorption is rapid, with peak blood-levels reached in 2-4 hours.[5] Unusually high blood-levels are maintained over a 24-hour period, which may be due to the loose binding of novobiocin by serum proteins and the reabsorption of antibiotics excreted by the liver. The blood levels are reported as being 10-50 times as high as that attained by equal doses of other antibiotics when therapeutically active amounts are administered. Novobiocin is well distributed throughout the body tissues and fluids but is usually not detected in the cerobrospinal fluid. Excretion studies show that about one-third of the antibiotic is excreted in the faeces *via* the bile. Approximately 3% is detected in the urine.

The April issue of *Antibiotic Medicine* contains 8 reports of the results of the clinical use of novobiocin. Most of the authors gave oral doses of 1-2 g. per day to adults. Children received 15 mg. per kg. per day. Transient generalized skin-reactions occurred in 0·5% of cases who received 1·0 g. per day. No serious side-effects such as staphylococcal enteritis or moniliasis were recorded.

Staphylococcal infections in particular responded readily. Martin *et al*[6] found novobiocin highly effective in the treatment of 4 of 5 patients with staphylococcal septicaemia. All 5 cases of staphylococcal enteritis responded, as well as 3 of 4 cases of skeletal-system infections.

Pyogenic infections of the skin, due mainly to staphylococci and streptococci, responded well[7].

Morton *et al*[8] treated 41 cases of soft-tissue infections with novobiocin in conjunction with surgery; the incidence and magnitude of the surgical procedures were reduced. Limson and Romansky[9] treated 30 cases of bacterial pneumonia; all the patients recovered, despite the existence of severe complicating conditions in 12 of them.

Satisfactory results were obtained in a number of cases of urinary infections due to susceptible strains of *Proteus vulgaris* and *E. coli*, though the latter is relatively insensitive to novobiocin.[10]

Further clinical studies are necessary to determine all the possibilities of novobiocin, but at this stage it appears to be a very useful antibiotic to use in the treatment of infections due to staphylococci, streptococci, pneumococci and proteus organisms.


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## WMA 10TH GENERAL ASSEMBLY

The 10th General Assembly of The World Medical Association will meet in Havana, Cuba, on 9-15 October 1956, at the Latin American Culture House. Delegations from more than 30 national member associations and observers from numerous international and national associations will attend.

*The Business Agenda* will *inter alia* include the following items: (1) The Second World Conference on Medical Education, Chicago, 30 August to 4 September 1959, (2) Hospital Organization and Administration and Medical Care in Latin America, (3) Central Repository for Medical Credentials, (4) International Emblem for Doctors in Civil Defence, (5) International Code of Medical Law.

*The Scientific Session* will consist of 2 symposia, viz.:

1. *Pathology in Prematurity*: (*a*) Causes of Death of the Premature in Cuba, (*b*) Infections of the Premature Infant, (*c*) Erythroblastosis and Kernicterus, (*d*) Haemorrhagic Disturbances of the Premature.

2. *Cardiovascular Surgery*: (*a*) Cardiovascular Surgery in Cuba, (*b*) Tetralogy of Fallot, (*c*) Pulmonary Stenosis, (*d*) Interauricular Communication, (*e*) Mitral Stenosis, (*f*) Anaesthesia in Cardiovascular Surgery.

*The Medical Editors' Conference* will deal mainly with Pan-American Medical Publication Problems.

A discussion will also be held on the Role of the Medical Profession in Medical-Care Plans.

# RADIO-ACTIVE ISOTOPES IN MEDICAL SCIENCE

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## 1. NATURE AND MEASUREMENT OF RADIO-ACTIVE ISOTOPES

The phenomenon of radio-activity has always excited the interest and imagination of the medical profession. The therapeutic value of radiations emitted by uranium and radium was recognized soon after the discovery of these elements at the turn of the present century. Hevesy realized, as long ago as 1923, that radio-active elements could be put to a different use in biology. The substance known as Radium D is, in fact, a radio-active form of lead and Hevesy used it to study the uptake and distribution of lead in plants and later in animals, tracing the element by virtue of its radio-active emanations.[1] Further applications of this method were limited by the fact that, although over fifty radio-active isotopes occur naturally, nearly all are heavy, rare metals of little biological importance. The artificial production of radio-active forms of common, light elements—first achieved by Irene Curie and Joliot in 1934—extended the range of biological problems which could be investigated by tracer techniques. With the splitting of the uranium atom and the construction of the first atomic pile at the University of Chicago in 1942 radio-active forms of all elements in undreamt of variety became available for biological and other uses.

The application of these radio-active isotopes to physiological, biochemical, and clinical problems has proved so fruitful that knowledge already gained through their use and their potential applications to diagnosis, therapy and research must now command the interest of every medical man. It is, however, difficult for those not familiar with isotope techniques to assess the significance of 'tracer' investigations and to visualize applications of value in their own fields of interest.

The present paper has been written in an attempt to provide general orientation concerning the nature and properties of radio-active isotopes and the methods commonly employed for their measurement. In the second part of this communication the general scope of the isotope technique in medical science will be outlined.

### NATURE OF RADIO-ACTIVE ISOTOPES

*Structure of the atom*[2]

The atomic nucleus which contains almost the entire mass of the atom consists of protons which carry unit positive charge and neutrons which are uncharged. The electrons in the uncharged atom are equal in number to the protons, carry unit negative charge, and move in definitely placed orbits around the central nucleus. The number of protons determines the chemical properties of the element and is referred to as the atomic number (Z) written as a subscript before the chemical symbol, e.g. $_{1}H$, $_{6}C$. The atomic mass (A) is the number of protons and neutrons and is written as a superscript either before (British convention) or after (American convention) the chemical symbol. It is apparent that the atomic number and chemical symbol are synonymous and the former is usually omitted, e.g. the various forms of carbon are written $^{12}C$, $^{13}C$, $^{14}C$ (British) or $C^{12}$, $C^{13}$, $C^{14}$ (American).

*Stable Isotopes*

It has long been known that certain elements exist in different forms which, although identical in every chemical and in most physical characteristics, do not have the same atomic weights—for example, there are 3 forms of lead having atomic weights of 206, 207 and 208. To such elements Soddy in 1913 gave the name isotopes, indicating atoms which are identical in regard to the number of protons (and electrons) and hence in regard to their chemical properties, but different in regard to their number of neutrons and their atomic weights. Many elements have only one stable form (e.g. $^{23}Na$, $^{31}P$), but the majority consist of mixtures of stable isotopes and this explains why many atomic weights are not whole numbers (e.g. magnesium 24·32, chlorine 35·457).

Study of the atomic configuration of the elements reveals that there are only certain specific combinations of protons and neutrons which give rise to stable atomic nuclei. Thus, for example, the nucleus of carbon, which contains 6 protons, is stable only when associated with 6 or 7 neutrons—hence the 2 stable isotopes of carbon found in nature—$^{12}C$ and $^{13}C$—of which the latter comprises 1·1% of naturally occurring carbon.

*Radio-active Isotopes*

A radio-active isotope differs from the stable forms of the element in that the neutron to proton ratio is unstable. The atomic nucleus tends to return to a stable configuration by rearrangement of its particles and this is associated with radio-active emission. Thus, for example, carbon atoms containing 6 protons and either 5 or 8 neutrons are unstable—hence the radio-active isotopes of carbon, $^{11}C$ and $^{14}C$.

Radio-active isotopes are artificially produced by the interaction of a small number of fundamental particles with the stable nuclei of the elements. In the cyclotron the target nucleus is bombarded with charged particles which are accelerated to high velocity by an oscillating electromagnetic field. By this means, for example, $^{23}_{11}Na$ (stable sodium) can be made to combine with a deuteron particle ($d$), which consists of a neutron and a proton ($p$). This compound nucleus retains the neutron, but immediately ejects a proton so that $^{23}_{11}Na$

is converted to the radio-active isotope of sodium, $^{24}_{11}$Na. Such reactions are conventionally written in abbreviated form

$$^{23}_{11}\text{Na (d, p) } ^{24}_{11}\text{Na},$$

i.e. the target nucleus is written first followed in parenthesis by the reacting particle and the emitted particle, and finally by the product nucleus. The production of radio-active isotopes in the cyclotron may involve transmutation of elements. Bombardment of $^{23}_{11}$Na with alpha particles ($\alpha$), which consist of 2 neutrons and 2 protons, leads to the production of a compound neucleus from which a proton is immediately lost, leaving a radio-active isotope of magnesium

$$^{23}_{11}\text{Na } (\alpha, \text{ p}) \, ^{26}_{12}\text{Mg}.$$

The practical advantage of such transmutation reactions lies in the fact that the product is chemically different from the target and can be separated from it. By this means it is possible to obtain isotopes of high specific activity—that is, containing a high degree of radio-activity per unit mass—or even 'carrier-free', which means that all the atoms in the product element are radio-active.

Large-scale production of radio-active isotopes only became possible with the development of the nuclear reactor (atomic pile), in which the target element is bombarded by neutrons. When $^{235}$uranium absorbs a neutron it undergoes fission into 2 smaller fragments and, at the same time, liberates a number of neutrons, which may be used to split further uranium atoms (chain reaction) so that the number of available neutrons multiplies progressively. Some of these neutrons may be allowed to escape from the reacting mass and be used for target bombardment. The neutron is uncharged and hence experiences no repulsion on approaching a target nucleus. The possibility of neutron capture is dependent mainly on the time it lingers in the vicinity of the nucleus and this is related inversely to the velocity of the neutron. In the atomic pile neutrons which are liberated at high velocity during uranium fission are slowed by passage through materials of low atomic weight—such as deuterium or graphite—before they are allowed to reach the target element.

Neutron capture may transform the target element into a radio-active form of the same element, e.g.

$$^{37}_{17}\text{Cl (n, } \gamma) \, ^{38}_{17}\text{Cl},$$

or lead to transmutation, e.g.

$$^{14}_{7}\text{N (n, p) } ^{14}_{6}\text{C}.$$

Such reactions have made it possible to produce at least one radio-active isotope of every element. At the present time over 1,200 isotopes are available for the 96 common elements; about 80% are radio-active and the great majority of these are artificially produced.[3]

*Decay of Radio-active Isotopes*

As indicated above the phenomenon of radio-activity is exclusively a property of the atomic nucleus. Unstable combinations of neutrons and protons tend to undergo rearrangement towards a stable configuration. This process which is often referred to as nuclear disintegration or radio-active decay may be accomplished by:

1. Emission of a negative beta particle from a neutron, leading to transformation of the neutron into a proton. An example of this form of decay is provided by radio-active $^{32}$phosphorus which emits negative beta particles and is converted to stable sulphur:

$$^{32}_{15}\text{P (radio-active P)} \rightarrow ^{32}_{16}\text{S (stable S)} + \beta^-$$

The atomic weight is unchanged by this decay process, since beta particles have negligible mass equivalent to that of the electron. These particles leave the nucleus at a velocity approaching that of light and are thought to arise from the atomic nucleus only during disintegration. Beta particles vary considerably in their energy, but can never penetrate more than a few mm. through tissues. It follows that in biological work $\beta$ radiations can be measured in blood and tissue samples, but cannot be detected at the body surface when emitted from deep, internal structures.

2. Emission of a positive $\beta$ particle (positron), leading to the transformation of a proton into a neutron; e.g.

$$^{11}_{6}\text{C (radio-active C)} \rightarrow ^{11}_{5}\text{Bo (stable Bo)} + \beta^+$$

The positron differs from the $\beta^-$ particle in that it carries positive charge and has only an ephemeral existence, rapidly undergoing combination with a negative electron, as a result of which both particles are annihilated and 2 gamma rays are emitted at 180° to each other.

3. Combination of a proton with an electron, leading to transformation of the proton into a neutron. This is referred to as K electron capture and is followed by a rearrangement of the remaining electrons in their orbital shells—this process being associated with X-ray emission; e.g.

$$^{37}_{18}\text{A (radio-active A)} \rightarrow ^{37}_{17}\text{Cl (stable Cl)} + \text{X-rays}$$

4. Emission of an alpha particle. This occurs only in elements having an atomic number greater than 82 and is of little importance in biological work. Alpha particles consist of 2 neutrons and 2 protons, are about 8,000 $\times$ the mass of beta particles and can penetrate only a few microns through body tissues.

5. Emission of gamma rays. Alpha or beta particle emission may leave the atomic nucleus in an excited energy state so that the further emission of one or more gamma rays is required to restore the ground state. Gamma rays consist of electromagnetic quanta (photons) which are uncharged and travel at the speed of light. They originate within the nucleus, but are otherwise similar to X-rays and have great penetrating power. For this reason gamma-emitting isotopes lodged in deep-lying tissues are readily detected *in vivo* by recording equipment placed at the body surface.

There are thus radio-active isotopes which are pure alpha, beta or gamma emitters; in addition, many combine various types of radiation—such as beta-gamma emitters (Table I). Both the type of emission and the energy of radiation are characteristic for each radio-active isotope.

*Rate of Radio-active Decay*

It is apparent from the above discussion that radio-active atoms continually undergo disintegration, during which process radiations of various types are emitted and atoms of stable nuclear configuration are formed. A fundamental attribute of this decay process is that its rate cannot be influenced by either chemical or physical means. The number of disintegrations occurr-

ing per unit time is proportional to the number of radio-active atoms present and is not dependent upon the age of any individual atom.

When the intensity of radiation has dropped to half its initial value, the number of radio-active atoms is reduced to half the number originally present. The time required for this diminution is termed the half-life ($t_{\frac{1}{2}}$). Each isotope has a characteristic half-life (Table I) and there is considerable variation, even among isotopes of the same element—for example,

TABLE I. CHARACTERISTICS OF SOME RADIO-ACTIVE ISOTOPES COMMONLY EMPLOYED IN BIOLOGICAL WORK

| *Element* | *Radio-active Isotope* | *Type of Radiation* | *Half-life* |
|---|---|---|---|
| Hydrogen .. | $^{3}H$ (tritrium) | beta | 12·1 year |
| Carbon .. .. | $^{11}C$ | positron | 20·5 min. |
| | $^{14}C$ | beta | 5,700 year |
| Sodium .. .. | $^{22}Na$ | positron, gamma | 2·6 year |
| | $^{24}Na$ | beta, gamma | 14·8 hour |
| Phosphorus .. | $^{32}P$ | beta | 14·3 days |
| Sulphur .. .. | $^{35}S$ | beta | 87·1 days |
| Chlorine .. .. | $^{36}Cl$ | K capture, positron, beta | $10^{6}$ year |
| | $^{38}Cl$ | beta, gamma | 37 min. |
| Potassium .. | $^{42}K$ | beta, gamma | 12·4 hour |
| Calcium .. .. | $^{45}Ca$ | beta | 180 days |
| Iron .. .. | $^{59}Fe$ | beta, gamma | 47 days |
| Cobalt .. .. | $^{60}Co$ | beta, gamma | 5·3 years |
| Iodine .. .. | $^{131}I$ | beta, gamma | 8 days |

various isotopes of cobalt have half-lives varying between 18 hours and 5 years. The rate of radio-active decay is obviously a matter of considerable practical importance in biological experiments. Isotopes having extremely short half-lives (e.g. $^{128}$iodine—25 minutes; $^{18}$fluorine—112 minutes) can be used only by laboratories close to the source of production and for experiments of short duration. On the other hand, isotopes having very long half-lives (e.g. $^{11}$carbon—5,700 years) are convenient from the analytical point of view, but carry the danger for the recipient of prolonged tissue irradiation. Unfortunately, radio-active isotopes of the commonest organic elements are either very short-lived or very long-lived. Thus, the two radio-active isotopes of carbon have half-lives of 20 minutes ($^{11}C$) and 5,700 years ($^{14}C$), radio-active hydrogen (tritrium—$^{3}H$) has a half-life of 12½ years and the radio-active isotopes of nitrogen and oxygen decay too rapidly to be of any practical use. For this reason the rare stable isotopes of these elements are frequently used in biological work, their presence being detected by means of the mass spectrometer.

## MEASUREMENT OF RADIO-ACTIVITY

The quantitative determination of radio-activity is based upon measurement of the ionization produced in media traversed by radiations. The most generally useful methods are those which measure the ionization produced in gases. Passage of charged particles through a gas leads, by electrostatic interaction, to the production of ion pairs consisting of heavy positive ions and negative electrons. Uncharged gamma and X-rays produce ionization only through collision mechanisms and for this reason detection of these rays by ionization tubes is less efficient than for beta particles.

Gaseous ions are unstable and have a marked tendency to recombine. However, if the ionization occurs in an electric field the electrons are accelerated rapidly towards the anode and the heavy positive ions move more slowly towards the cathode. The imposed electric field may be of such strength that only those electrons liberated by passage of the ionizing particle are collected and measured. In such an instrument, which is known as an ionization chamber, the total amount of ionization within the sensitive volume of the counter is measured. If the strength of the imposed electric field is increased (Fig. 1), the electrons initially liberated by the ionizing

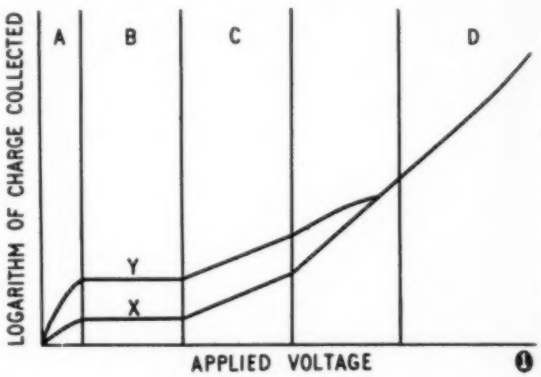


*Fig.* 1. Diagramatic representation of the relationship between the applied voltage and charge collected at anode in a counting tube. Curve X—result obtained when ray or particle produces a small number of ion pairs. Curve Y—result obtained when a large number of ion pairs are produced by ray or particle.
Region A—some ions lost by re-combination.
Region B—all the ions initially formed are collected and measured (ionization chamber).
Region C—multiplication of ions proportional to initial ionization and applied voltage (proportional counter).
Region D—multiplication of ions unrelated to initial ionization (Geiger-Muller counter).

radiations are accelerated to such a degree that they cause ejection of other electrons, leading to multiplication of the initial charge by as much as 10 orders of magnitude. Voltages leading to such multiplication of the initial charge are used in Geiger-Muller and proportional counters, which are widely employed for the measurement of beta particles.

Ionization in a Geiger-Muller tube (Fig. 2) is followed by a period known as the 'dead time' during which the counter cannot respond to a second ionizing particle; this introduces an error at counting rates of above 5,000 per minute. The dead time can be reduced by filling the tube with a mixture of a monatomic and polyatomic gas, the latter being referred to as a quenching gas. Argon and ethanol are commonly used, with the latter supplying about 5% of the total pressure 5-40 cm. mercury. Such tubes have a finite life because with each discharge some of the polyatomic gas is broken down into smaller particles which do not have 'quenching' properties.

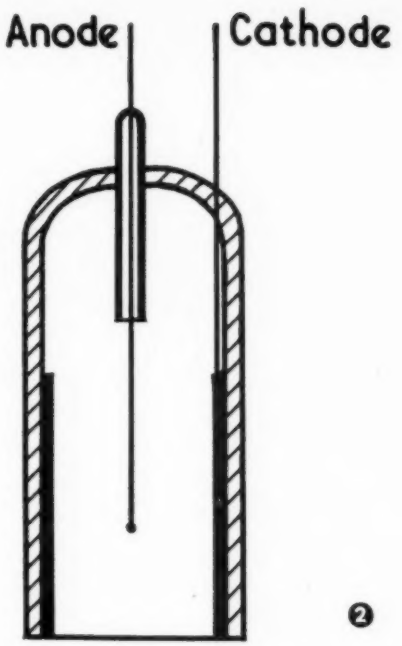


*Fig.* 2. Diagram of Geiger-Muller tube having a thin end-window permitting the entry of low-energy beta particles.

Proportional counters are operated at lower voltages than Geiger-Muller tubes and have the advantage of a very much shorter 'dead time', so that counting rates of up to 100,000 per minute are possible. In addition, they are operated at atmospheric pressure, so that the sample can be conveniently introduced into the counter before the counting gas is pumped into the sensitive volume of the tube.

Scintillation counting is dependent upon the production of fluorescence by the ionizing particle or ray. Substances having the property of fluorescing in the presence of radio-activity are called phosphors. Lord Rutherford used the method of counting flashes of light in a zinc-sulphide phosphor to obtain the data on which was based his theory of the atom. In modern scintillation counters a sodium iodide-thallium crystal is commonly used as the phosphor. In addition, a variety of organic phosphors are now available in crystalline, plastic or liquid form; in the last-mentioned the radio-active sample can be dissolved in the phosphor itself. With the development of the photomultiplier tube, which enables light flashes emitted by the phosphor to give rise to detectable electrical impulses, scintillation counting became an effective and convenient method of radio-active assay especially valuable for counting gamma radiations.

The electrical discharges from counting tubes or from the photomultiplier of the scintillation counter are too rapid to operate a mechanical register directly. For this reason the pulses are first passed through an electronic scaling circuit which records a known number of impulses before activating the mechanical register, which may respond to only 1 out of 1,000 discharges from the counter.

*Corrections in Radio-active Assay:*

All methods for the assay of radio-active isotopes are sensitive to the ionization produced by cosmic rays and the natural radio-activity of the earth's surface. These sources of ionization produce what is called a background counting-rate, which is measured by operating the counter without exposure to a known source of radio-activity; this value is subtracted from the gross rates obtained with samples. The background limits the sensitivity of the instrument and can be reduced by suitable shielding of the counter, with lead.

The radio-activity of samples analysed is also corrected, on the basis of the half-life of the isotope, for physical decay occurring during the course of the experiment. Any observed reduction in radio-activity is then attributable only to such biological processes as dilution of the labelled compound by the body 'pool' or catabolism of labelled molecules and replacement by newly-synthesized unlabelled ones.

Since a radio-active source emits radiations in all directions it is apparent that only a portion of the ionizing particles or rays will enter the counter. This proportion is determined mainly by the geometrical relationship of the sample to the counter. In addition, in beta decay some particles travelling away from the counter are reflected back from the material on which the sample is mounted and may enter the tube (back scattering). Other beta particles will be absorbed in the window of the counter, in the air between counter and sample, or in the sample itself. The last-mentioned is known as self-absorption and is dependent on the energy of the beta particles and the weight of the sample per unit area. Samples are said to be of 'infinite thickness' when particles emitted by the lower parts are completely absorbed in the upper so that only the top layers contribute towards the observed counting-rate. Under these circumstances self-absorption is constant and can be neglected.

It is apparent that the radio-activity of samples must be measured under strictly constant conditions during the course of any experiment. By measuring standard samples of known radio-activity under the same conditions it is possible to determine the efficiency of the method and convert measured counting-rates into units of radio-activity.

*Units of Radio-activity*

The original unit of radio-activity was called the curie and was defined as the quantity of radon in equilibrium with one gram of its parent radium. Later the definition was changed to indicate the absolute radio-activity of one gram of radium ($3{\cdot}7\times10^{10}$ disintegrations/sec.). With the advent of artificial isotopes the curie was adopted as the unit for all radio-active sources and now indicates the amount of a radio-active isotope which contains $3{\cdot}7\times10^{10}$ disintegrating nuclei/sec. This unit is too large for tracer experiments and has therefore been subdivided into the milli-curie ($3{\cdot}7\times10^{7}$ disintegrations/sec.) and the micro-curie ($3{\cdot}7\times10^{4}$ disintegrations/sec.).

Another unit, the rutherford ($10^6$ disintegrations/sec.) has been proposed but has not met with general acceptance.

### PREPARATION OF ISOTOPES FOR BIOLOGICAL WORK

It is necessary for biological purposes that the isotope be administered in appropriate chemical form and, in some cases, with the labelled element in a specific position in the molecule. In most instances conventional chemical methods are used for synthesis. However, many compounds of biological importance are prepared by means of biosynthesis—for example, plants exposed to $^{14}CO_2$ are used for the preparation of labelled sugars and pharmacological compounds such as nicotine and morphine, while algae grown in an atmosphere of labelled $CO_2$ are a source of various organic compounds including proteins and amino acids. Another method of preparing labelled compounds consists in the bombardment of the unlabelled substance with neutrons in the atomic pile. This procedure is usually unsuccessful because the energy liberated in nuclear reactions leads to rupture of chemical bonds within the molecule. However, it has been possible by this procedure to label the cobalt atom of vitamin $B_{12}$ without destroying the biological activity of the vitamin.[4]

At the present time a great variety of labelled compounds of biological importance are available from the Atomic Energy Commission in the USA and the Radiochemical Centre in England. In the current catalogue of the latter, for example, more than 120 $^{14}$carbon-labelled compounds are listed and the range of available products is constantly being extended.

## II. GENERAL SCOPE OF THE ISOTOPE TECHNIQUE

The fundamental assumption underlying the use of radio-active isotopes is that, apart from the emission of radiations, their physical and chemical behaviour is identical with that of naturally occurring forms of the elements. This assumption is not always completely valid and observed differences are referred to as 'isotope effects'. These differences are concerned mainly with the energies of activation and the velocities of chemical reactions,[5] but are relatively minor in extent and for practical purposes can usually be ignored in biological work.

Methods employed for radiation detection respond to the decay of single atoms, so that as little as 1/1,000th microgram of a radio-active element may be sufficient for analysis. This remarkable sensitivity makes it possible to employ extremely small 'tracer' doses of isotopes and so to study the fate of labelled compounds in the organism without disturbing the natural equilibrium. It is not surprising that an analytical method having these unique properties should have found application in every branch of biology and taken a place among the standard procedures of clinical medicine.

In the consideration of the general scope of the isotope technique in medical science applications of the method will be divided into 4 categories dependent upon:

1. Localization of the labelled compound.
2. Measurement of dilution of the labelled compound.
3. Measurement of incorporation of labelled compounds into bodily constituents and 'turn-over' of such labelled constituents.
4. The therapeutic value of radiations.

### LOCALIZATION OF LABELLED COMPOUNDS

The distribution of specific elements and compounds among various tissues of the body has been established by classical methods of chemical analysis. Thus, for example, potassium is known to be localized predominantly within cells, sodium and chloride are mainly extracellular, while certain elements such as iodine are highly concentrated in specific tissues. Radio-active isotopes by virtue of the sensitivity and ease of their measurement provide a convenient method of studying the distribution of compounds in the body. In addition, tracer methods constitute a unique means of investigating dynamic exchanges between tissues under conditions which do not disturb the natural equilibrium.

The chemical exchanges which occur across capillaries and the endothelium of the gastro-intestinal tract as well as between cells and their fluid environment have been extensively studied with the aid of tracer methods. It has been found in many instances that previously observed net exchanges are associated with an extremely rapid transfer of materials in both directions. Thus, the well-known 'chloride-shift' which occurs in erythrocytes during gas transport is superimposed upon a rapid exchange of this ion in both directions across the red-cell membrane.[6] During absorption of sodium and chloride from the gastro-intestinal tract these ions also pass freely from the circulating plasma into the intestinal lumen.[7] One of the most elegant applications of the isotope technique has been the demonstration of the fact that passage of a nerve impulse is associated with an increased movement of potassium outward and of sodium inward across the axon membrane leading to a transient accumulation of sodium within the nerve fibre.[8, 9, 10]

The tracer method has revealed that exchanges across capillary walls between intra- and extra-vascular compartments occur with extraordinary rapidity. A volume of water equal to the total amount present in the body is lost from the plasma every twenty minutes and is replaced by water from extra-vascular fluid, while 60% of the sodium and chloride present in the circulation is exchanged each minute.[11, 12] Plasma proteins pass out of the plasma more slowly, about 5% of circulating albumin leaving the blood-stream each hour.[13, 14] Traumatic shock does not appear to be associated with a generalized increase in capillary permeability, but there is considerable leakage of plasma protein in damaged areas,[15, 16] while injured cells become freely permeable[17] and may accumulate a large proportion of the body sodium, which is then unavailable for exchange with other tissues.

Following the administration of gamma-emitting isotopes the distribution of radio-active material can be traced by means of counters placed at the body surface. This technique forms the basis of several procedures which have proved to be of considerable clinical value. The simplest test of thyroid function using radio-iodine is the determination of the percentage of the isotope taken up by the gland within 24 hours of administration.[18] By means of an automatic scanning counter the size and functional activity of the thyroid can be mapped after injection of $^{131}$iodine, the functional status of thyroid nodules determined, and metastatic thyroid tissue demarcated.[18] Circulatory efficiency in vascular disease can be assessed by comparing the counting rate over the affected region with that of an apparently normal area after the intravenous administration of radio-active sodium or labelled serum-albumin.[19] In addition, measurement of the rate of blood flow between two defined points or the rate of removal of radio-active material from intramuscular or subcutaneous sites provide a hitherto unobtainable over-all picture of circulatory efficiency.[20] Similar methods can be used to test the circulation in pedicle skin-grafts[21] and to determine the cardiac output.[21]

Rapidly proliferating cells may take up certain radio-active compounds more rapidly than normal tissues. There have been many attempts to make use of this phenomenon in localizing tumours of the liver[22, 23] and brain.[24] However, localization by means of gamma-emitting isotopes is liable to considerable error and with cerebral tumours the positron emitter, $^{72}$arsenic, is likely to prove of greater value.[25] As stated previously, the positron undergoes an annihilation reaction when it combines with an electron and during this process two gamma rays are produced which emerge at 180° to each other. The use of a counter sensitive only to these coincident radiations allows the axis on which the tumour lies to be defined and by mapping two axes the site of the tumour can be fixed with some certainty.[26, 27]

## ISOTOPE DILUTION

The isotope-dilution technique, which was first employed by Hevesy to measure the lead content of an ore, is a convenient and accurate means of determining the total amount of a specific substance present in a complex chemical mixture. A labelled form of the material to be determined is added in known amount and after complete mixing a small quantity of the material is isolated and purified. The degree of dilution of the tracer isotope provides a measure of the amount of the material originally present.

This method has been used in the analysis of many compounds of biological importance. Thus for example, the amino-acid content of haemoglobin,[28] B-lacto-globulin[29] and various enzymes[30] has been measured by isotope dilution. The same principle has been extensively used to estimate the volume of various fluid compartments of the body and the mass of specific chemical substances present in the living subject.

A basic requirement of such estimations is that isotope dilution should be calculated at a time when the label is uniformly mixed throughout the compartment or chemical substance under investigation. This may require prolonged observation and in some cases may be impossible to achieve. The volume of dilution of $^{82}$bromine, for example, which is thought to be confined to extracellular fluid, expands significantly between 4 and 24 hours after administration to healthy adults, so that measurements of the extracellular space based on shorter periods of observation are erroneously low.[31] Moreover, it is probable that complete mixing of labelled bromine with the extracellular fluid is even slower in oedematous subjects.[32] Injected labelled-sodium is rapidly diluted by the sodium in the plasma and extracellular fluid and then for a period of 24 hours undergoes a further progressive dilution by exchange with the sodium of bone, which contains some 30% of the total quantity in the body. Thereafter no further dilution occurs, despite the fact that the isotope has exchanged with only about 45% of the total bone sodium. Thus, the isotope-dilution technique provides a measure of body sodium which excludes about half of that present in the skeleton;[33] this quantity is usually referred to as the 'total exchangeable sodium'. The dilution of radio-active potassium at 24 hours accounts for about 98% of the potassium present in the body, and excludes only a small amount in erythrocytes and bone which exchanges relatively slowly.[33] An accurate estimate of the total plasma-protein content of the body is difficult to obtain because labelled protein molecules enter the extravascular compartment relatively slowly and do not attain a stable and uniform distribution between plasma and lymph.[34]

A second basic requirement of the method is that the degree of isotope dilution should be measured at a time when the labelled compound is confined to the compartment or chemical substance under investigation. The rapid exchanges which occur among components of the body's metabolic pool make this difficult to achieve in many instances. Labelled glucose, for example, is rapidly converted into those chemical intermediates which lead to the formation of glycogen or oxidation to carbon-dioxide and water, so that estimates of the 'glucose pool' are considerably in excess of the total amount of free glucose present in the body.[35, 36] The use of tritrium($^3$H)-labelled water[37] over-estimates the total body-water by about 2%, because the label exchanges with the hydrogen of the hydroxyl groups of carbohydrate and peptide bonds of protein.

Despite these limitations, which are due either to incomplete mixing or failure of the label to remain confined to the space or chemical substance measured, the isotope-dilution technique undoubtedly constitutes an analytical method of considerable clinical value—and one which is particularly useful in studying the constitution of the body fluids (Table II). Its application

TABLE II. BODY CONTENT OF WATER AND TOTAL EXCHANGEABLE SODIUM, POTASSIUM, CHLORIDE AND ALBUMIN, MEASURED BY ISOTOPE DILUTION IN HEALTHY HUMAN ADULTS

| | |
|---|---|
| Total Body Water | 44-70% of body-weight[24] |
| Extracellular Fluid | 14-17% of body-weight[32] |
| Potassium | 24-54 mEq./kilo body-weight[24] |
| Sodium | 24-46 mEq./kilo body-weight[24] |
| Chloride | 34-54 mEq./kilo body-weight[38] |
| Albumin | 2·1-4·5 g./kg. body-weight[13] |

in pathological states has emphasized the fact that it is frequently impossible to assess the body content of a component from its plasma level. Serum-sodium concentration, for example, is frequently low at the time when the total body-sodium is increased, and the reverse relationship is often true of potassium.[33]

### INCORPORATION AND TURN-OVER STUDIES

The use of isotopes has undoubtedly found its most fundamental application in the study of intermediary metabolism. Ingested substances rapidly lose their identity in the body and it is impossible to discover what proportion has been stored, oxidised, or used in synthetic processes. By means of isotopic labelling, however, the fate of dietary compounds can be followed and the nature of the relatively simple precursors used by the tissues for synthesizing complex organic molecules can be established. By this means it has been shown, for example, that the creatine of muscle is built up from 3 amino acids—arginine, glycine and methionine,[39] that the haem pigment of haemoglobin is derived largely from glycine,[40, 41] and that acetate is the main precursor of cholesterol, which is synthesized almost exclusively in the liver.[42] Significant progress has also been made in elucidating the pathways of hormone synthesis in the adrenal cortex,[43] adrenal medulla,[44] and thyroid gland.[45] Studies of isotope incorporation have demonstrated the remarkable capacity of tissues for building up complex molecules from relatively simple precursors and have revealed that, in general, circulating proteins and lipids are not directly used in synthetic processes.

Before the introduction of isotope techniques the chemical constituents of tissues were regarded as being relatively inert, undergoing only slow 'endogenous' processes of catabolism, while ingested 'exogenous' compounds were thought to be almost completely broken down to yield the energy required by the body. The fallacy of this concept was revealed by the classical experiments of Schoenheimer and Rittenberg,[46] who demonstrated that even in animals on a deficient caloric intake an appreciable proportion of dietary fat was deposited in the fat depots. Since there was no corresponding increase in the mass of body fat it was evident that the constant deposition of adipose tissue was balanced by an equal rate of mobilization from the fat depots. Moreover, it was evident that fat oxidised at any time must be a mixture of dietary and tissue fat which had merged together in a common 'metabolic pool'. Later experiments with labelled amino acids revealed that tissue and dietary proteins are in a similar state of dynamic exchange, the rate of which varies considerably in different organs of the body. Proteins of liver, intestinal mucosa, kidney, spleen and plasma have been estimated to be completely replaced about once every 2 weeks in man;[47] the protein of muscle and skin, on the other hand, exchanges relatively slowly, while that of collagen is almost completely inert.[48]

These findings have given rise to the concept of 'turn-over', indicating the dynamic processes of synthesis and catabolism which underlie the maintenance of steady state conditions in the body. Turn-over studies involve observation of the rate of decline of radio-activity in a particular constituent following its initial labelling by means of an isotope. The exchangeable protein pool can be labelled, for example, by the intravenous injection of a tracer dose of $^{14}$carbon[49] or $^{131}$iodine-labelled[50, 51] plasma-protein and the subsequent decay of radio-activity measured on serial samples of plasma (Fig. 3).

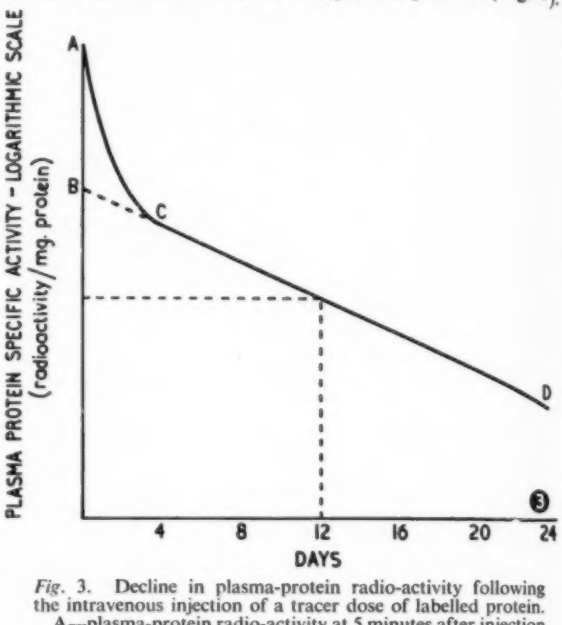


*Fig.* 3. Decline in plasma-protein radio-activity following the intravenous injection of a tracer dose of labelled protein.

A—plasma-protein radio-activity at 5 minutes after injection—the labelled molecules have mixed completely with the circulating blood, but have not escaped from the circulation.

AC—rapid decline in radio-activity due to mixing of labelled molecules with extravascular protein of lymph and tissue fluids.

CD—slower decline in radio-activity due to metabolic break-down of plasma protein and replacement by newly-synthesized, unlabelled molecules.

B—plasma-protein radio-activity which would have been observed had the injected labelled molecules mixed instantaneously with the entire exchangeable protein pool. The biological half-life is the time taken to reach half the value B, i.e. the time taken for half the molecules in the exchangeable pool to be catabolised and replaced (in this instance, 12 days, i.e. a turn-over of 5·8% of the exchangeable pool per day).

From such observations the 'biological half-life' is readily determined, i.e. the time taken for the level of radio-activity to fall to half the initial value obtained after complex equilibration. Red blood-cells labelled with radio-active chromium have a biological half-life of between 25 and 40 days in normal subjects.[52] A considerable shortening of the red-cell half-life is observed in haemolytic states as well as in some patients in whom there is no chemical or clinical indication of increased red-cell destruction.[53] Fibrinogen and beta-lipoprotein normally have a very much more rapid turn-over than albumin or gamma globulin. It is surprising that in cases of hepatic cirrhosis the biological half-lives of plasma proteins do not appear to be significantly altered.[54] It must be emphasized that the calculation of absolute rates of synthesis and catabolism

from the biological half-life may be misleading—especially when the labelled compound enters into many different metabolic processes or is not uniformly distributed between the various compartments of the exchangeable pool.[55]

### THERAPEUTIC VALUE OF RADIATIONS

Several radio-active isotopes such as $^{60}$cobalt, $^{90}$strontium and $^{137}$caesium, which is a waste product of the atomic reactor, have been employed as external or locally implanted sources of radiation. These are to be regarded as potent substitutes for X-radiation and radium therapy—$^{60}$cobalt, for example, is 35 times more radio-active (gram for gram) than radium. Other radio-active isotopes employed for therapeutic purposes are administered internally—a method initiated by the work with $^{131}$iodine in thyroid disease[56, 57] and $^{32}$phosphorus in leukaemia and polycythaemia.[58, 59] These two isotopes have particular therapeutic value because they are selectively concentrated in specific tissues—$^{131}$iodine in the thyroid gland and $^{32}$phosphorus in all rapidly dividing cells, including those of the bone marrow. Partial or complete ablation of the thyroid in hyperthyroidism can be achieved with radio-active iodine,[60, 61] while polycythaemia vera can be brought under effective control with $^{32}$phosphorus,[62, 63] which also has a measure of usefulness in chronic leukaemia.[64]

Internally administered radio-active isotopes may expose tissues throughout the body to potentially damaging radiations. This type of therapy therefore requires a thorough assessment of dosage distribution based upon knowledge of the physical half-life of the isotope employed, the nature and energy of its radiations and the metabolic fate of the labelled compound injected. Radio-active manganese, for example, is rapidly removed from the bloodstream and accumulates transiently in the liver and pancreas before being excreted into the gastro-intestinal tract. By injecting an isotope of manganese having a half-life of only 2·6 hours it is possible to obtain emission of about 96% of the radiation in liver and pancreas. The possibility of employing this isotope in the treatment of hepatic and pancreatic malignancies is being investigated.[3]

A new experimental approach to the problem of localizing the effects of irradiation is under investigation at the Brookhaven National Laboratory, where a technique known as neutron-capture therapy[3, 65] has been elaborated. A stable element which will readily capture a neutron and become radio-active is administered by intravenous injection and the appropriate region of the body is then exposed for a short period to slow neutron bombardment in a nuclear reactor. The element rendered radio-active is one in which decay is almost instantaneous and the range of radiation produced limited to a few microns. The rare stable isotope of boron (atomic mass 10) readily absorbs a neutron and immediately thereafter emits an alpha particle. Boron is concentrated in cerebral-tumour tissue so that its intravenous administration followed by neutron bombardment of the head liberates extremely potent alpha particles confined to the neoplasm itself; a series of patients with glioblastoma multiforme have been experimentally treated in this way with encouraging results.[66]

### CONCLUSION

It will be evident from the examples quoted above that isotope techniques have been of great academic and practical value in many branches of medical science. New tools of investigation are often applied with over-zealous enthusiasm and with the isotopes it is necessary to remember that more direct methods can often be used to obtain the same information. Nevertheless, isotopes will be preferred in many instances—not because they are indispensible, but on account of greater convenience and sensitivity. It should also be borne in mind that although isotopes can be measured with remarkable precision, this does not imply that the results of tracer experiments are any less fallible than those obtained by other means. Tracer studies can seldom be interpreted in isolation, and successful application of the method is almost invariably based upon information derived from other chemical and physiological techniques of investigation.

Radio-active isotopes have contributed in one unique and outstanding way to medical science. It is impossible to visualize how the remarkably rapid exchanges which occur in both directions between the components of plasma and extracellular fluid and between cells and their chemical environment could ever have been measured without the use of isotopically labelled compounds. In this field of study the isotope technique has revolutionized the concepts of biological investigators and, in the future, will undoubtedly supply new standards of clinical measurement of considerable practical value.

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# NEPHRO-COLIC FISTULA AS A COMPLICATION OF PROSTATECTOMY

J. A. CURRIE, M.S. (LOND.), F.R.C.S. (ENG.)

*Cape Town*

Nephro-colic fistula was first described by Hippocrates in the 5th century B.C. A clearer and more complete account was published by Rayer in 1841. Mertz,[8] in 1931, collected 42 cases of reno-visceral fistula. Of these 29 were nephro-colic. An excellent account by Vermooten and McKeown,[12] with a review of the literature, followed in 1933, and since then reports and reviews have been fairly numerous. In 1949 Abeshouse[1] published a very complete and comprehensive account of fistulae between the upper urinary tract and other viscera, as well as various cutaneous fistulae. His very extensive bibliography should be consulted by those interested. The series reported included 89 nephro-colic fistulae.

More recently Briggs and Neale[4] and Ellik and Getz[5] have published cases and brief reviews. The latter authors collected 54 cases and added 2 of their own, bringing the total to 56. They did not refer to Abeshouse's collection of 89 cases. Finally, Glenn S. Rost *et al.*[10] published a case estimated to be the 90th, but did not refer to the articles by Briggs and Neale,[4] and Ellik and Getz.[5] Apparently the total should really be 93. This brief survey illustrates the difficulty of being certain how many cases of any particular condition have been reported.

Nephro-colic fistula is relatively uncommon, and most authors record only one, or perhaps two cases. Wesson,[13] however, was able to report 3 personal cases, all referred to him by one surgeon.

It is probable that the condition will become progressively less common owing to earlier diagnosis, the use of antibiotics, and the fact that few modern patients will tolerate the pain and fever of a severe renal infection without seeking early advice.

In the case now reported, the fistula was only discovered during treatment for prostatic obstruction.

A nephro-colic fistula is the most frequently occurring type of communication between a kidney and a hollow viscus. In Mertz' series, 2 were nephro-gastric, 2 reno-duodenal, 9 nephro-bronchial and 29 nephro-colic. Of the 29 nephro-colic fistulae, there was a direct communication between kidney and colon in 20 cases, with no intervening fistulous track. In Abeshouse's larger collection of 226 cases, nephro-colic fistulae were preponderant.

The commonest aetiological factor is a pyogenic renal infection, with or without calculi. Ratcliffe and Barnes[9] analysed 37 cases. Of these, 5 were due to calculous pyonephrosis, 18 to pyonephrosis without calculi, and only 5 to tuberculosis. In Abeshouse's 89 cases,[1] 25 were of tuberculous origin.

The rarer reno-duodenal fistula, of which 9 cases have been recorded, are slightly more frequently due to tuberculosis (4 cases in 9), according to reports by Jones, Melendy and Flynn,[7] Bloom,[3] and Glaser.[6]

Hydatid disease of the kidney is a rare cause of nephro-colic fistula. Abeshouse records 3 cases, of which 2 were mentioned by Campbell Begg.[2]

I have been able to find only one report of a nephro-colic fistula due to a renal carcinoma (Thompson and Douglas)[11] and cases due primarily to bowel disease are apparently unknown.

*Course*

The course of the illness is usually prolonged. The classical signs and symptoms of a perinephric abscess may resolve, and blood, pus or urine may appear in the faeces. Pneumaturia or obvious faecal contamination of the urine may occur, but usually gross urinary infection is all that is observed. Urine, or even urinary calculi, have been detected in the faeces.

*Diagnosis*

The diagnosis rests finally, as a rule, on retrograde pyelography. In only 6 recorded cases has a barium enema revealed the fistula. Good examples of the success of retrograde pyelography have been published by Mertz,[8] Vermooten and McKeown,[12] Ratcliff and Barnes,[9] and Ellik and Getz.[5] In the case described by Rost *et al*,[10] pneumonephrosis first suggested the diagnosis, colonic gas making a complete pyelogram.

In Wesson's first case[13] there was a cutaneous fistulous opening through which an opaque medium was injected from the loin. This case was interesting in that the huge tumour was diagnosed as a hypernephroma and treated by X-rays. After a voluminous haemorrhage the mass disappeared, but the haematuria persisted. After 8 X-ray treatments this ceased; the patient was well for 9 years, and the case was reported in the literature as a radiological cure of a renal growth. Then an abscess in the flank ruptured spontaneously and led to the diagnosis and treatment of a nephro-colic fistula.

The passage of profuse watery stools, and the appearance in them of indigo-carmine injected intravenously, led to the correct diagnosis in a case described by Ellik and Getz.[5] In their other case, aortography revealed a scanty blood-supply to the left kidney. A retrograde pyelogram demonstrated the fistula. I cannot see that the aortogram provided strikingly useful information.

*Treatment*

The treatment of this condition is to remove the kidney and, if possible, to close the fistula by direct intervention. Owing to dense and cartilage-like adhesions around the kidney, the operation is difficult and sometimes dangerous. Ratcliff and Barnes[9] found the mortality of operation to be 33% and emphasized the value of conservative treatment. Briggs and Neale,[4] writing 14 years later, are much more radical, and advocate an abdominal approach, and resection of both the kidney and the involved segment of gut. This seems unnecessarily severe. Several authors stress the fact that a faecal fistula may occur after a nephrectomy done through the loin, but add that it soon closes. In some cases a perinephric abscess or gross pyonephrosis may require drainage before the final radical operation. Rost's case occurred in a man with only one kidney, and a conservative operation was successful.

The removed kidneys are usually mere remnants, with replacement of renal tissue by fat and fibrous tissue. The histological findings suggest chronic inflammation, with granulomata and large necrotic areas surrounded by epithelioid cells, and a dense fibrous outer layer. Foreign-body giant-cells may be present, but tuberculosis is diagnosed in only a minority of the cases.

In the case to be described, the fistula was only discovered after a prostatectomy performed in two stages for acute retention with gross urinary infection.

## CASE REPORT

Mr. C.P., a well-built vigorous man aged 56 years, was admitted to the Military Hospital, Wynberg, in January 1951. He gave a long history of difficulty with micturition, he had acute retention with an over-distended bladder, and his urine was grossly infected. Drainage with a urethral catheter was instituted, and an intravenous urogram was done. The right kidney was normal, the left was non-functioning, and the cystogram showed a grossly trabeculated bladder.

On 3 January a suprapubic cystostomy was done. Unfortunately I omitted to follow my usual practice of performing bilateral vasectomy. The convalescence was complicated by left-sided pain and fever, attributed to a perinephric abscess, but the symptoms disappeared after treatment with penicillin. At a subsequent cystoscopy, it was found impossible to catheterize the left ureter owing to the size of the prostate.

In March 1951 a second-stage retropubic prostatectomy was performed, and an easily enucleable adenoma weighing 120 grams was removed. Recovery was uneventful, but the urine remained turbid. The urinary stream was entirely satisfactory. Cystoscopy was deferred and the patient was treated with sulphadrugs and antibiotics.

He was readmitted in September 1951 with a urinary infection with B. proteus, and epididymitis. The latter occurrence made me regret that I had not performed vasectomy. An intravenous pyelogram revealed, as before, a normal right kidney and a non-functioning left kidney (Fig. 1). At cystoscopy the bladder was

Fig. 1.

Fig. 2.

Fig. 3.

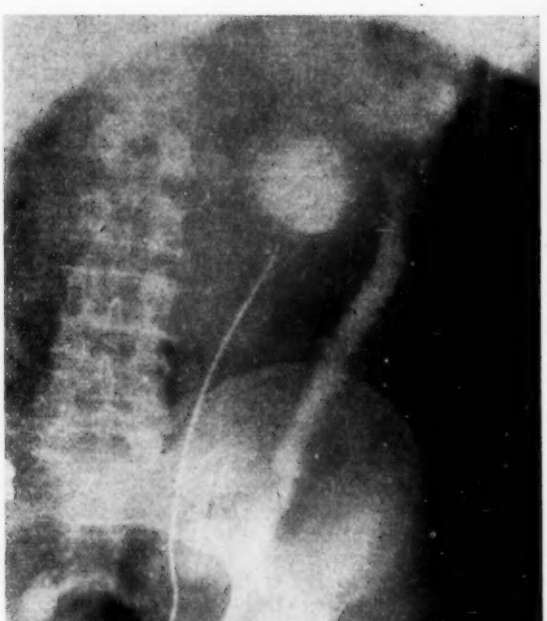


Fig. 4.

still trabeculated but otherwise normal. The left ureter was catheterized and retrograde pyelograms clearly demonstrated a nephro-colic fistula (Figs. 2, 3 and 4).

*Operation*, 9 September 1951. The kidney was exposed. Dense adhesions and cartilage-like masses of fibrous tissue made exposure very difficult. Eventually the ureter was found, freed, divided and turned up in an attempt to reach the renal pedicle. Further efforts resulted in the opening of a very foul abscess, which was drained. A finger exploring the cavity determined that it was a large renal pelvis, and the dilated calyces could be felt.

*Post-operative course*. The patient made an excellent recovery. The urine immediately became clear and has remained so ever since. The patient returned to his work as a dockyard policeman, did it excellently, and was able to indulge in outdoor amusements, including sea-bathing. The cavity had to be drained with a Foley

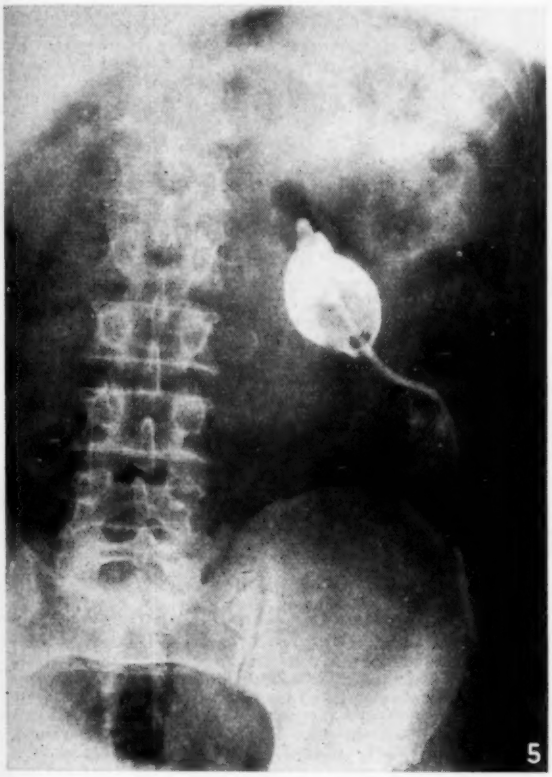

Fig. 5.

catheter, which was changed every 3 weeks (Fig. 5). The average daily drainage was ½ oz. of thin purulent fluid. For various reasons the patient was allowed to continue at work, always healthy and efficient, but always needing drainage, until 1954.

Attempts were made by injecting various substances to close the cavity. Streptokinase, streptodornase, eusol, and sodium morrhuate were used. These all failed and, in fact, seemed to start an infection with B. pyocyaneus. Eventually the kidney was removed.

*Operation*, 27 January 1954. Dissection of cutaneous fistula. Resection of 11th rib (note absence of 12th rib). The renal fossa was approached below the diaphragm without opening the pleura. An adherent mass of fat containing the cavity and the renal pelvis was dissected out with great difficulty. A plaque of thinned renal tissue the size of a shilling was left attached to the colon. The wound was closed with drainage. No actual nephro-colic

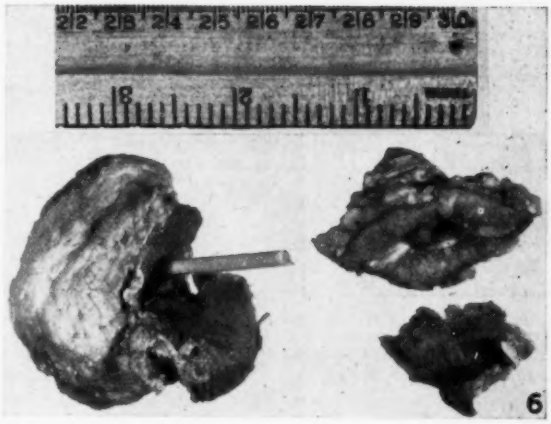

Fig. 6.

fistula was identified. The patient recovered rapidly and has been quite well ever since. The resected mass (Fig. 6) was examined histologically. The appearances are those of chronic inflammation and not those of tuberculosis.

## *Comment*

This fistula was due, as most of such fistulae are, to a renal infection. There was no antecedent history of renal disease and the patient was admitted to hospital originally for prostatic obstruction.

The rather leisurely handling of this case may be criticized. No retrograde pyelogram was done until 6 months after the prostatectomy. It was impossible before this operation, inadvisable just after it, and was later deferred owing to the patient's excellent condition and desire to remain at work. After the first kidney-operation the patient lived and worked for over 2 years with a Foley catheter in his side, before the radical operation was done. This may seem unduly dilatory. The patient was, however, very fit, was unwilling to undergo yet another operation, and knew that it might be a severe one. It is possible that the prolonged drainage was responsible for the closure of the internal fistula, leaving merely a cavity with an external opening.

Other points of interest are the excellent demonstration of the fistula by retrograde pyelography, the disappearance of all evidence of urinary infection when the ureter was divided, and the absence of even a transient faecal fistula after the final operation.


## SUMMARY

The literature of nephro-colic fistula (and other renal fistulae) is reviewed and a case is reported.


My thanks are due to the Senior Medical Officer, R.N., Simonstown, and to the Commanding Officer, No. 2 Military Hospital, Wynberg, for permission to publish this case.

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# SQUALENE FROM HUMAN SEBACEOUS CYSTS

F. W. HOUGEN, PH.D.

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Čmelik[1] failed to find squalene in the lipids of human sebaceous cysts using the usual hydrochlorination method.

Wheatley[3] recorded that human epidermal cysts contained no squalene.

Squalene has now been detected in surgical specimens of human (European) sebaceous cysts as described below. The unsaponifiable matter (1·16 g.) of the lipids of sebaceous cysts (170 g.) was chromatographed on activated alumina (10 g. Peter Spence, Type H) and the hydrocarbon fraction eluted with hexane was dissolved in dry ether and saturated with an excess of dry hydrogen chloride.[2] Evaporation of the ether left a solid (0·1 g.) which after crystallization from acetone had m.p. 123-135° [Found: C, 57·65; H, 9·1; Cl, 33·6%. Calculated for $C_{30}H_{56}Cl_6$: C, 57·2; H, 9·0; Cl, 33·8%]. The hydrochloride had an infra-red spectrum ($CHCl_3$ solution, 2·5-12·5 $\mu$) identical with that of an authentic specimen of squalene hexahydrochloride mixed isomers. It did not depress the melting point (125-135°) of the latter.

All of the eluates of the above chromatogram fluoresced in ultra-violet light, but had very low and non-specific absorption in the ultra-violet. Polycyclic aromatic hydrocarbons are therefore present in very minute amounts, if at all, by contrast with the appreciable amounts found in human hair wax.[4]

The author is indebted to Dr. E. J. Schulz, Pretoria General Hospital, for collecting the cysts.

This paper is published by permission of the South African Council for Scientific and Industrial Research.

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# REGULATIONS CONTROLLING MEDICAL USE OF RADIO-ACTIVE ISOTOPES

In Government Notice No. 1650 of 7 September 1956 the following regulations made by H.E. the Governor General under section 31 of the Atomic Energy Act No. 35 of 1948, as amended, are gazetted under the title 'Regulations in connection with the Use of Radio-active Isotopes for Medical Purposes'.

## REGULATIONS

1. In these regulations—

(*a*) 'A-dose' means a dose greater than 50 microcuries or a dose consisting of an isotope with a half-life longer than 30 days;

(*b*) 'B-dose' means a dose equal to or less than 50 microcuries and consisting of an isotope with a half-life of 30 days or less; or such dose consisting of a specific radio-active isotope and having such maximum activity as the Atomic Energy Board may specifically approve;

(*c*) 'qualified hospital physicist' means a person who—

(i) holds a degree of Master of Science in physics, and has obtained 1 year's training in clinical hospital physics at a training institution or hospital approved for this purpose by the Atomic Energy Board; or

(ii) holds an honours degree of Bachelor of Science in physics, and has gained 2 year's training in clinical hospital physics at an institution approved for this purpose by the Atomic Energy Board; or

(iii) holds a degree of Bachelor of Science in physics and has undergone such training or gained such experience as the Atomic Energy Board may deem equivalent to the requirements set out in (i) and (ii) above;

(*d*) 'qualified radiotherapist' means a person who—

(i) holds a degree or diploma in radiotherapy which is recognized by the Atomic Energy Board; or

(ii) holds a recognized degree or diploma in radiology which includes training in both diagnosis and therapy, on condition that the person concerned shall produce documentary evidence that he or she has gained a further full year's experience in the therapeutic application of radio-active isotopes at an institution approved by the Atomic Energy Board; or

(iii) holds qualifications in radiology, when the person concerned can produce evidence to the satisfaction of the Atomic Energy Board that he has undergone training and gained experience which is equivalent to the requirements set out in sub-paragraphs (i) and (ii) above;

(*e*) 'committee' means the committee of control over the use of radio-active isotopes established by the Board in terms of section 14 of the Act;

(*f*) 'Board' means the Atomic Energy Board, as established in terms of section 11 of Act No. 35 of 1948;

(*g*) 'radio-active isotopes' means the radio-active isotopes of any element other than radium and its disintegration products;

(*h*) 'Act' means the Atomic Energy Act, No. 35 of 1948, as amended by Act No. 18 of 1952, as further amended by Act No. 11 of 1956.

2. The Board shall issue to every person recognized by it as a qualified radio-therapist or qualified hospital physicist a certificate to the effect that he has been recognized as such.

3. The Board may grant to hospitals and institutions a general authority to administer A-doses, on condition that the hospital

or institution appoint a local committee of control over the use of radio-active isotopes, such committee to be constituted as follows:

(*a*) Chairman: The head of the department of radiology or the head of the department of radiotherapy, where such departments are organized separately.

(*b*) Member: A qualified radiotherapist.

(*c*) Member: A qualified hospital physicist.

(*d*) Member: A pathologist.

(*e*) Member: A physician.

The first-mentioned 3 members shall constitute the executive of the local committee of control and shall be responsible for the daily decisions in respect of the use and handling of radio-active isotopes at the hospitals or institutions.

4. The appointment of each member of a local committee of control shall be approved by the Board in writing.

5. With the approval of the Board a hospital or institution may nominate a qualified radiotherapist who is in its part-time service as a member of the local committee of control.

6. Before a general authority can be granted to a hospital or institution it shall have at its disposal the services of a full-time qualified hospital physicist.

7. The Board shall have the power, where it may deem it necessary, to require the appointment of an additional qualified hospital physicist before it grants or renews an authority.

8. Before the Board grants an authority in terms of regulation 3, it shall satisfy itself that the hospital or institution has at its disposal the necessary equipment and facilities for the safe and efficient handling, storage, removal or disposal of radio-active isotopes.

9. The Board may, where it deems it necessary, for the safe and efficient use, handling, storage and removal or disposal of radio-active isotopes, by means of written notice of at least 30 days, require the hospital or institution to improve or enlarge its equipment and/or facilities.

10. There shall be placed at the disposal of the qualified hospital physicist a room in which he can handle, store, monitor, assize or dispose of small quantities of radio-active isotopes. This room shall be protected against any interference from external stray irradation while small (tracer) quantities of radio-active isotopes, which have been administered to patients, are monitored.

11. The qualified hospital physicist shall also be provided with a room to the satisfaction of the Board for the handling of large quantities of radio-active isotopes.

12. All survey instruments and dosimeters shall be calibrated at least once in every 6 months by a person or institution authorized thereto by the Board.

13. The calibrating officer or institution shall issue to the hospital or institution in whose use the instruments are, a certificate whereon the survey instruments and/or dosimeters which have been calibrated by him are shown, as well as the date of the calibration.

14. Patients in whose bodies the equivalent of an A-dose is contained, shall be accommodated in separate wards, exclusively reserved for such patients. The Board shall be empowered in the case of certain treatments which may be prescribed, to grant exemption from this regulation.

15. The wards mentioned in regulation 14 shall, to the satisfaction of the Board, be equipped with facilities for the storage and disposal of radio-active isotopes, the storage of clean and radio-active bedpans, bottles and other equipment, and for the handling of dirty linen and contaminated articles.

16. The wards shall provide sufficient protection to staff members against external irradation.

17. All persons working with radio-active isotopes shall be provided with pocket dosimeters as well as film badges obtainable from the film badge service of the C.S.I.R.

18. All local control committees shall annually, on 30 September, submit to the Board a report containing the following information:

(*a*) Particulars of the radio-active sources in the possession of the institution.

(*b*) Particulars of the equipment and hospital facilities available.

(*c*) Particulars of the medical practices followed in the different therapeutic administrations at the institution.

(*d*) Particulars of the physical practices followed, including the method of standardizing equipment.

(*e*) A list of the members of the local committee of control.

19. A qualified radiotherapist in private practice may be authorised by the Board to administer A-doses at a hospital or institution on condition that it is done under the supervision of the local committee of control appointed at the institution or hospital in terms of regulation 3.

20. (*a*) The Board may grant limited authorities for the administration of A-doses to institutions, firms or qualified radiotherapists in private practice where they are not able to establish a local committee of control as required by regulation 3, on condition, however, that—

(i) the medical administration of the radio-active isotope is done under the direct control of a qualified radiotherapist; and

(ii) a qualified hospital physicist is available on a full-time basis.

(*b*) Where the Board is satisfied that the administration of A-doses can be undertaken with the assistance of a part-time qualified physicist, an authority may be granted on such conditions as the Board may deem fit.

21. Limited authorities for the administration of A-doses shall be subject to such of the conditions laid down in regulations 8, 10, 12, 13, 14, 15, 16, 17 and 18 as the Board may determine.

22. Authorities to administer B-doses may be granted by the Board where it has been satisfied that the applicant has at his disposal the necessary equipment and accommodation facilities for the proper handling, storage and disposal of radio-active isotopes.

23. The Board, shall, as prescribed by section 15 of the Act, appoint a suitably qualified person to carry out inspections of the premises and equipment of applicants for and holders of authorities to hold and use radio-active isotopes, in order to determine whether the equipment and/or accommodation comply with the provisions of these regulations and generally whether they are suitable and efficient for the proper and safe handling of radio-active isotopes.

24. The officer referred to in regulation 23 shall have the right at all reasonable times to enter the premises of applicants for or holders of authorities in order to determine whether the accommodation facilities are suitable, the equipment suitable and efficient, as well as to observe whether the practice employed in the administration of radio-active isotopes complies with the provisions of these regulations and, in general, is safe.

25. Any applicant for an authority or any of his employees who handles radio-active isotopes shall if required by the Board, submit himself for examination by the Board or a person authorised thereto by the Board in order to determine whether the applicant or any of his employees possess the necessary knowledge and/or experience to handle radio-active isotopes.

26. The Board shall cause to be compiled guides regarding the practice to be followed, as well as lists of the minimum requirements of equipment and facilities which it deems necessary for the handling of radio-active isotopes. These guides and lists shall be attached by the Board to each authority or renewal of an authority issued by it.

27. Any authority issued in terms of these regulations may be cancelled by the Board—

(*a*) where the institution or any of its employees contravenes any provision of these regulations; or

(*b*) where, owing to unforeseen circumstances or conditions, the cancellation of the authority is considered by the Board to be in the public interest.

28. All authorities granted in terms of these regulations shall lapse on 30 September of each year, and all holders of authorities must, at least 30 days before the authorities lapse, apply for the renewal thereof.

29. Any person who contravenes these regulations or fails to comply with them, shall be deemed to have contravened or failed to have complied with a condition upon which an authority has been granted to him under section 3 of the Act, and shall be subject to the penalties prescribed by section 33 of the Act.

# RESEARCH FORUM, UNIVERSITY OF CAPE TOWN

At the meeting of Research Forum held at Groot Schuur Hospital, Cape Town, on 4 September 1956, 3 papers were read on the subject of Porphyria and Porphorins, of which abstracts follow:

## PORPHYRIA—CLINICAL EXPERIENCE IN CAPE TOWN

By Dr. L. Eales

The exact frequency of this disease in South Africa is unknown but it is already a major medical problem. This report is concerned with 66 cases, of which 5 were from institutions other than Groote Schuur Hospital. There were 38 Europeans, 23 Cape Coloured, and 5 Bantu patients. The disease as it is seen in the European and the Cape Coloured races is inherited as a Mendelian dominant characteristic and has varying modes of expression. In accord with Dean, cases of the 'cutanea tarda' form, the acute abdominal and/or neurological forms and symptomless porphyria have been found in one and the same family. There were only 5 Bantu cases and in only one was a suggestive family history obtainable.

Up to 1950 the author was able to find records of only 7 cases, but since then there has been a marked increase: 1951-4, 1952-9, 1953-15, 1954-12, 1955-9, and in the first 6 months of 1956-5. These were all new cases. There have been several readmissions. This increase in incidence has been due to improved diagnostic acumen. The European patients, with the exception of 3 (a German, a Hollander and an Irishman), were all of Afrikaner stock.

The salient clinical features were described in detail and illustrated with slides. The variability of the course of the disease was stressed, in particular in relation to the assessment of the effects of therapy.

With the advent of corticotrophin and the steroid drugs it was hoped that an effective therapy was at hand. These hopes have not been realized. Cortisone has been administered to 12 patients, ACTH to 1 and Prednisone to 3. Dramatic improvement in a case of the acute abdominal form followed on cortisone in 1 case. Improvement also occurred in one other, but in the remainder it was extremely doubtful whether cortisone exerted any beneficial effect, and death from ascending paralysis occurred in 2 patients while on cortisone. Two patients with extensive 'cutanea tarda' lesions (one with severe secondary scleroderma-like changes) showed no striking improvement.

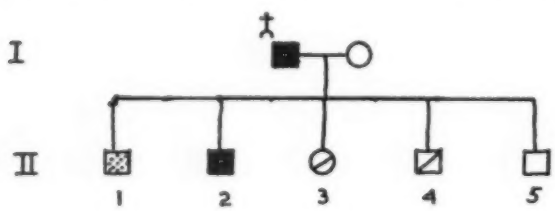
Prednisone was of no material benefit to 3 patients receiving it. In one patient a first course seemed to lead to improvement but the second course was associated with a gross deterioration in the patient's condition and the treatment was stopped.

Extensive studies on the daily excretion of porphyrin in the urine have been carried out by Prof. G. C. Linder in collaboration with whom patients in this hospital have been studied. The improvement that followed cortisone in the 2 cases cited above was accompanied by a precipitous fall in urinary porphyrin output (from 60 mg. to 3 mg. per day) but similar falls have been observed in other patients undergoing spontaneous improvement. The severity of the symptoms in the acute abdominal and/or neurological forms could frequently be correlated with the output of urinary porphyrins, but this was not invariable.

## A REPORT ON A COLOURED FAMILY WITH PORPHYRIA

By Dr. E. B. D. Dowdle

This is a local Cape Coloured family which Dr. Dowdle investigated earlier this year. The father died of acute porphyria at the age of 34 years without having had skin lesions of any description, according to the wife. The wife is normal in all respects with a normal faecal porphyrin content (11·2μg/g. dry weight of stool). There are 5 living sibs, of whom one (II, 1) has cutaneous porphyria with no acute manifestations whatever, one (II, 2) has acute porphyria with no cutaneous lesions, two (II, 3 and 4) have no other abnormality than an increased porphyrin content in the stool, and one (II, 5) is normal in all respects.




This indicates quite clearly that the presence of the abnormal gene in the genetic constitution of the individual may express itself either as acute porphyria, porphyria cutanea tarda, or a mixture of the 2 forms, or by the increased excretion of porphyrin in the stool of an otherwise normal person. Blood-group studies were also carried out on these patients as proof of legitimacy and in the hope of detecting some linkage in the inheritance of the disease, which could be of help in giving genetic advice to the relatives of sufferers. No evidence of illegitimacy was found. It is too early to draw any conclusions from the results of these studies, but it is hoped that this work will be extended.

## EXPERIENCE WITH A RAPID SCREENING TEST FOR STOOL PORPHYRINS

By Dr. S. J. Saunders

Method: A knife-edge of wet stool was dissolved in about 3 ml. of a solution consisting of equal parts of amyl alcohol, ether and glacial acetic acid. This was then placed in ultra-violet light and the degree of fluorescence recorded as 0, ±, +, ++, +++, or ++++. The negative result was a yellowish or green colour while the ++++ showed brilliant bright red fluorescence, the intermediate degrees being recorded accordingly.

Results: 297 stools from 237 patients were examined and of these 200 were negative. One important stool in this group came from a known case of porphyria who was experiencing some abdominal pain at the time and had porphobilinogen in his urine, which also fluoresced in ultra-violet light. Attention is drawn to the concept of the stool porphyrins falling as the urine porphyrins rise and *vice versa*. 36 were ± and 30 + and these groups comprised no porphyrics. 14 were ++ and this group comprised one porphyric. 11 were +++ with 3 porphyric stools. 6 were ++++, 5 of these being from cases of known porphyria and the 6th being obtained from a moribund patient who had porphobilinogen and uroporphyrin in his urine but had not up to that point been suspected of having porphyria. There was no relationship to race, sex, age, diet, liver disease or alcoholic intake in this series.

Conclusions: The results of this series indicate that a ++++ result is probably diagnostic of porphyria. Patients may have porphyria and have less than a ++++ result and even a negative result. The series will continue.

The next meeting of Research Forum will be held at 12 noon on Tuesday, 2 October 1956, in the A-Floor Lecture Theatre, Groote Schuur Hospital, Cape Town. Speakers: Dr. C. Merskey and Dr. H. Nossel. Subject: Blood coagulation studies after ingestion of fat. Visitors are welcome.

## IN MEMORIAM

### MAX GORFINKEL, M.A., M.D.

*Dr. P. Leftwich of Cape Town, writes:* Dr. Max Gorfinkel, who died in Cape Town on 5 August 1956, received his early education at the South African College School, where he had an outstanding career. His contemporaries still speak of his exceptional brilliance as a schoolboy, being year after year the top scholar of his class. He proceeded from school to the University of Cape Town, having been awarded an exhibition and the South African High Schools prize, and there studied for the Medical B.A. degree. His academic history from this time on was a catalogue of the honours awarded him. In 1919 he gained the class medals for physiology, comparative anatomy and bacteriology. He was appointed senior lecturer in anatomy at the University of Cape Town Medical School during 1921 and graduated M.A. Anatomy in 1922. With the proceeds of the Croll Memorial Travelling Scholarship he proceeded to Glasgow University, where he graduated M.B., Ch.B. During his stay in Scotland, he continued true to form and was awarded the Mackintosh Bursary and medals in Pathology and Clinical Surgery. After a spell of house appointments in England, he spent a year as Medical Officer at the Anglo-Ecudorian Oilfields in Ecuador, acquiring there a knowledge of the Spanish language which he never lost and loved to use for many years afterwards.

Dr. Gorfinkel

Returning to Cape Town in 1928, he settled at Claremont and rapidly developed an extensive general practice. In 1938 he returned to the United Kingdom and did postgraduate work in London, Glasgow and Edinburgh, obtaining the Glasgow M.D. degree. In spite of the claims of a busy practice, his interest in clinical medicine was sufficiently intense for him to devote valuable time to academic work, and for 4 years he was Honorary Medical Registrar at Groote Schuur Hospital.

In 1948, after 20 years of general practice, he was registered as a Medical Specialist and remained in consulting practice until his death.

'Maxie', as he was affectionately known to his patients, friends and colleagues, had an outstanding career, but he was no narrow book-worm. He was a 'character' and, measured by most standards, he was an exceptional person. An excellent doctor, he was loved by his patients and earned their implicit trust by a combination of sound scientific method, deep psychological understanding, and his genius for fun and humour. Widely read in verse and prose, he loved to declaim the classics and to spice his conversation with a Latin tag or a Spanish phrase. He was an excellent raconteur, full of humour and unable to resist a propensity for clowning. A lover of good company and good food and wine, an evening with him was always a stimulating and amusing experience. He was a fine amateur fiddler, with a first-rate gift of musical appreciation, and was well known in the professional and amateur musical worlds of the Cape. As a student he was not too proud to turn an honest penny by playing in dance bands in Cape Town and Glasgow. Indeed, what with the proceeds of scholarships and his earnings as a musician, he was almost completely self-supporting for the duration of his student life.

The profession can ill afford to lose so gifted and human a colleague.

He is survived by his wife Pauline.

## PASSING EVENTS : IN DIE VERBYGAAN

*The next meeting* of Research Forum, University of Cape Town, will be held at 12 noon on Tuesday, 9 October 1956 in the A-Floor Lecture Theatre, Groote Schuur Hospital, Cape Town. Speakers Dr. C. Merskey and Dr. H. Nossel. Subject, Blood coagulation studies after ingestion of fat.

* * *

*International Labour Organization, Geneva.* Experts from 11 countries met in Geneva in August to consider the classification and labelling of dangerous substances with 5 symbols warning workers of danger from explosion, fire, corrosion, poisoning and radiation.

Rehabilitation: Discussions also took place in August at Geneva on the subject of rehabilitation between Mr. David A. Morse, Director General of ILO and Dr. Howard A. Rusk, chairman of the department of rehabilitation and physical medicine, and Dr. Eugene J. Taylor, assistant professor of clinical physical medicine and rehabilitation, New York University.

* * *

*Die Tak Wes-Kaapland* van die Mediese Vereniging van Suid-Afrika nooi met genoë alle lede en hul vrouens wat op 3 Oktober 1956 in Kaapstad is, na die verdaagde Algemene Jaarlikse Vergadering van die Vereniging wat op daardie datum plaasvind. By hierdie geleentheid sal die pas-bevestigde President, dr. J. S. du Toit, sy Voorsittersrede lewer. Ere-erkennings sal ook aangebied word. Die vergadering sal in die Jamiesonsaal, Universiteit Kaapstad, om 7.45 n.m. vir 8.15 plaasvind. Kleredrag formeel of akademies. Musiek en verversings. Wees asseblief so goed, indien u van plan is om teenwoordig te wees, om die Tak-Sekretaris, Posbus 643, Kaapstad, voor 1 Oktober daarvan in kennis te stel, sodat die nodige reëlings vir verversings getref kan word.

* * *

*Railway Medical Officers Group—Annual General Meeting.* The Annual General Meeting of the Railway Medical Officers Group, will be held at the System Manager's Board Room, Railway Station, Cape Town, on Monday, 1 October 1956, at 8.30 p.m. sharp.

* * *

*Dr. I. N. Marks*, who has been working in the Western General Hospital, Edinburgh, has left to work in America. His address is now at the Fels Research Institute and Temple University Hospital, Philadelphia 40, Pa., USA.

* * *

*The Atlas Assurance Company Ltd.*, has indicated that members' malpractice policies are now, without extra premiums being payable, extended, within certain limits, to cover the cost of legal defence against criminal charges.

* * *

*South African Society of Anaesthetists.* At the Annual General Meeting of the S.A. Society of Anaesthetists held on 26 August 1956, the following members were elected to the Council for the year 1956/57. President: Dr. R. A. Moore Dyke; Vice-President: Dr. O. J. Verster; Hon. Sec./Treasurer: Dr. Pen Wessels; Members: Drs. H. Bentel, F. J. Durham, C. Frost and H. Ginsberg; Area Representatives: Northern Transvaal: Dr. O. V. S. Kok;

Southern Transvaal: Dr. D. L. Jeffes; Western Cape: Dr. C. Jones; Immediate Past President: Dr. F. W. Roberts.

* * *

*South African Medical Congress, Durban, September* 1957. Members who intend to exhibit in the hobbies section of the Congress their own work or that of their families, are requested to communicate with the Secretary of the section, Dr. Julian S. Coller, Bigden House, 505 Smith Street, Durban.

* * *

*Clinical Meeting—Pretoria.* A clinical meeting is to be held in Pretoria on Saturday afternoon and Sunday morning 13-14 October 1956, when the subject of 'Diabetes' will be exhaustively discussed.

In addition, an informal cocktail-dance will be held at the Pretoria Country Club from 6.30–10 p.m. on the evening of Saturday the 13th. The cost will be one guinea per couple and dress will be informal.

The programme will be as follows: Familial and Genetic Aspects of Diabetes—Dr. F. Ziady; The diagnosis as viewed by a G.P.—Dr. W. H. Lawrence; Some complications of Diabetes—Dr. P. J. Kloppers; Occular changes in Diabetes—Dr. N. L. Murray; Vascular disorders associated with Diabetes—Dr. Allan Glen; The Pregnant Diabetic—Dr. P. H. Oosterhagen; The Diabetic Child—Dr. L. Harris; The Anaesthetist views the Diabetic—Dr. O. V. S. Kok; The Treatment of Diabetes: (*a*) Dietetic aspects—Mrs. I. E. Rautenbach (Chief Dietician, Pretoria Hospital); (*b*) The use of Insulin—Dr. J. T. M. de Villiers; (*c*) Treatment of Coma—Dr. Japie du Toit; (*d*) The surgery of Diabetes—Prof. C. H. Derksen.

Will all members of the Northern Transvaal Branch who intend to be present at the clinical meetings and the social gathering, please inform the Hon. Secretary of the Branch as soon as possible. (Tel. 2-9741—136.)

* * *

*Kliniese Byeenkoms—Pretoria.* 'n Kliniese byeenkoms sal op Saterdagmiddag 13 Oktober en Sondagoggend 14 Oktober, in die Algemene Hospitaal, Pretoria, gehou word. Die onderwerp vir bespreking is ‚Diabetes'.

Op Saterdag aand sal 'n informele skemerparty-dans van 6.30—10 nm. in the Pretoria Buite-Klub gehou word, teen £1 1s. 0d. per paar. Aandete sal verskaf word en drag is informeel.

Die program vir die kliniese byeenkoms is as volg: Familière en genetiese aspekte van Diabetes—Dr. F. Ziady; Die diagnose uit die oogpunt van die Algemene Praktisyn—Dr. W. H. Lawrance; Verskeie Komplikasies van Diabetes—Dr. P. J. Kloppers; Okkulêre Veranderings in Diabetes—Dr. N. L. Murray; Vaskulêre aandoenings verbonde aan Diabetes—Dr. A. Glen; Die Swanger Diabetikus—Dr. P. H. Oosterhagen; Die Diabetiese Kind—Dr. L. Harris; Die Narkotiseur se opvattings i.v.m. die Diabetikus—Dr. O. V. S. Kok; Die Behandeling van Diabetes: (*a*) Dieëtkundige aspekte—Mev. I. E. Rautenbach; (*b*) Die Gebruik van Insulin—Dr. J. T. M. de Villiers; (*c*) Die Behandeling van Coma—Dr. Japie du Toit; (*d*) Chirurgie by Diabetes—Prof. C. H. Derksen.

Dit sal op prys gestel word indien alle geneeshere wie van plan is om die kliniese vergadering en/of die sosiale byeenkoms by te woon, aub. die Ere-Sekretaris van die Tak daarvan in kennis sal stel. (Tel. 2-9741—136.)

* * *

*Dr. John C. Thomas*, of Durban, has relinquished the post of Provincial Pathologist, Natal Provincial Administration, and is now Director of the Durban Blood Transfusion Service, Mark House, Mark Lane, Durban. Telephone 23423.

* * *

*The* 1956 *London Medical Exhibition* is to take place from 12-16 November at the Horticultural Hall, Westminster. Exhibits this year are more numerous than ever. A very extensive field of medical interest is covered, and the latest developments in ethical medical products will be shown as well as a most interesting and wide range of professional apparatus for the physician and surgeon. Some interesting modern hospital equipment will also be on view. A full programme of films of professional interest is arranged for each day of the exhibition.

Professional men and buyers from overseas are very welcome, and invitations may be obtained by writing to The Organizers, The London Medical Exhibition, 194-200 Bishopsgate, London, E.C. 2.

## NEW PREPARATIONS AND APPLIANCES : NUWE PREPARATE EN TOESTELLE

*Metreton Tablets and Nasal Spray.* Scherag (Pty) Ltd. announce their new products Metreton Nasal Spray and Metreton Tablets, and supply the following information:

Metreton Tablets contain 2·5 mg. of the corticosteroid prednisone (Meticorten) 2 mg. of the antihistamine chlorprophenpyridamine maleate (Chlor-Trimeton Maleate), and 75 mg. of ascorbic acid. Each c.c. of Metreton Nasal Spray contains 2 mg. (0·2%) of prenisolone acetate (Meticortelone Acetate) and 3 mg. (0·3%) of chlorprophenpyridamine gluconate (Chlor-Trimeton Gluconate).

*Advantages.* The combination of anti-allergic and anti-inflammatory agents with ascorbic acid is designed to afford more complete and rapid control of certain allergies than anti-histamines alone and to give prolonged relief because of the postulated protective action of ascorbic acid on circulating corticosteroids. The ascorbic acid is also of value in stressful conditions. Meticorten and Chlor-Trimeton are usually well tolerated and Metreton Tablets may be used without undue risk of electrolyte disturbance or undesirable anti-histamine effects. Metreton Nasal Spray provides rapid and prolonged relief from sneezing, nasal discharge, and congestion. Rebound engorgement and other effects often occurring in persons sensitive to sympathomimetic vasoconstrictors have not been noted with Metreton.

*Indications.* Metreton Tablets: Conditions such as severe hay fever, chronic asthma, perennial allergic rhinitis, atopic and contact dermatoses, exudative and inflammatory phases of ocular disorders.

Metreton Nasal Spray: Acute or chronic rhinitis, allergic rhinitis, polyposis (without fibrous change) associated with nasal allergy, reduction of oedema and inflammation in sinusitis or nasopharyngitis.

*Administration and Dosage.* Metreton Tablets: Initially one or two tablets after meals and at bedtime. When a satisfactory response is obtained, reduce to the minimum maintenance level and discontinue where possible.

Metreton Nasal Spray: Once in each nostril every 3 or 4 hours. For the first 24 hours more frequent use may be required. When the symptoms are satisfactorily controlled, frequency of application may be reduced.

*Packings.* Metreton Tablets, bottles of 30 and 100. Metreton Nasal Spray, 15 c.c. plastic 'squeeze' bottle. Manufactured in the Union of South Africa by Scherag (Pty) Ltd.—P.O. Box 7539, Johannesburg.

* * *

*Cirotyl.* Parke Davis Laboratories (Pty.) Limited, the South African subsidiary of Parke, Davis & Company, announce the introduction of Cirotyl, a laxative preparation containing diacetoxydiphenylisatin, a synthetic derivative of diphenylisatin, which has been identified as the active laxative principle of California prunes.

Cirotyl is not absorbed; its mode of action appears to be by contact with the intestinal mucosa, in contrast with other compounds such as anthraquinones and phenolphthalein, which act by contact with the mucossa as well as by absorption and re-excretion in the colon. The action of Cirotyl is gentle but persistent, similar to natural bowel movement.

Cirotyl is indicated for the prevention and treatment of occasional and habitual constipation; it is especially suitable for the prevention of constipation during convalescent or treatment periods with dietary restriction.

Each teaspoonful (4 c.c.) of Cirotyl contains 1·66 mg. of diacetoxydiphenylisatin in a palatable vehicle.

The following doses, which may be repeated, if necessary, within 24 hours or doubled on the following day are recommended: For infants ¼-½ teaspoonful, for children 2-5 years ½-1 teaspoonful, for children 5-10 years 1-2 teaspoonfuls, for adults and older children 1-3 teaspoonfuls.

The time between administration of the dose and evacuation is usually 6-8 hours.

Cirotyl is obtainable in bottles of 4 fl. oz.

## REVIEWS OF BOOKS : BOEKRESENSIES

### MEDICAL RESEARCH

*Medical Research: A Midcentury Survey.* Volume I. American Medical Research: in principle and practice. Volume II. Unsolved Clinical Problems: in biological perspective. Pp. (Vol. I xxxii + 765) (Vol. II xxxii + 740). 105s. per set. Boston—Toronto: Little, Brown and Company. 1955.

*Contents:* Volume I. *American Medical Research: in principle and practice.* Foreword. Introductory: Outlining why and how this study was made. 1. Medical Research in the Perspective of Biological, Chemical, Physical, Mathematical Science. 2. Current Trends and Current Problems in Medical and Biological Research in the United States. 3. Research Agencies. 4. Clearing Results and Controlling Products of Medical Research. Appendix. Volume II. *Unsolved Clinical Problems: in biological perspective.* 1. Current Metabolic Concepts Orienting Research in Biology and Medicine. 2. Cancer. 3. Infertility. 4. Arteriosclerosis. 5. Hypertension. 6. The Rheumatic Syndromes. 7. Tuberculosis. 8. The Nature of Viruses and of Virus Diseases. 9. Alcoholism. 10. Biology of Schizophrenia. Appendix.

It is well recognized that America has established a commanding lead in all fields of research. These two volumes show that this is not the result of chance but emerges from calculated endeavour. The American Foundation has as its objective, 'to set up defences against the lack of fact and the weight of particular propaganda that inhibit clear thinking on many important questions'. Following its numerous other fact-finding enquiries it sets down, in this report, the facts regarding research in biology, chemistry and physics in relation to the maintenance of high standards of medical education and of medical care for the whole population. Here we find the whole panoply of the American research scene—the magnificent structure is arrayed before us. Nay, it is dissected for our edification. Here we find pen-pictures of all the hundred-and-one institutions which contribute to the whole—they can only be 'snippets' or else these volumes would be monumental in size—the foundations (e.g. Rockefeller, Commonwealth, Macy and Carnegie), the Universities and Medical Schools, the independent endowed research institutes and the like; the financing of these agencies, and their difficulties as well as their achievements; the extent of Government support and responsibility, as well as the contribution of that other great American institution 'private enterprise'. In addition there is an evaluation of the significance of the various varieties of research and how they should be compared. The emphasis is always on fundamental research viewed in biological perspective, utilizing the contributions of chemistry, physics and mathematics and the results of research on atomic energy. Always the enquiry is how to further this research, how best to reorganize and support the institution, individual or project which is most worthy of this support.

In the second volume, 9 clinical conditions are discussed. These are cited merely as examples and there could be many more. They have been chosen because they exemplify some of the unsolved clinical problems which face us at this mid-point of the 20th century. No. attempt is made to present a comprehensive monograph on any one of these problems, for each of them could easily justify a volume or more on its own. Rather do they aim at reviewing current trends in fundamental research needed for understanding the mechanisms involved in the clinical state. Any success in any one of these conditions must immediately reflect on many of the others and on most biological problems. It is a tall order and because of its very magnitude can only succeed in the smallest degree.

It is not a book one can take up to pass an idle moment. It is largely a book for reference; it is a research project on the research scene. It will find its niche in libraries and in institutions whose function it is to sustain medical (and other) research and education. It is a contribution to knowledge, an analyses of fact, and a hope for the future. It is hardly likely to become a 'best seller', but it will not lie neglected on the library shelf.

C.M.

### THE CEREBROSPINAL FLUID

*The Cerebrospinal Fluid.* By S. Lups, M.D. and A. Haan, M.D. (Pp. 350 + xv. 52s. 6d.) London, Amsterdam, New York: Elsevier Publishing Co. Ltd. 1954.

*Contents:* 1. Anatomical and Physiological Observations. 2. The Puncture of the Cerebrospinal Fluid. 3. The Investigation of the Cerebrospinal Fluid as an aid in Diagnosis. 4. Methodology. Bibliography. Index.

This monograph, the first in the English language for some 15 years, supplements but does not replace, the classical works of Boyd, Greenfield and Carmichael, Cushing, Merrit and Freemont-Smith. It is a pity that the translators should have adopted such an unfortunate style to put across the ideas of the authors.

The book reviews the mode of formation and composition of normal and pathological fluids and the different methods used in their chemical and cytological analysis. The technique of lumbar puncture is treated in an orthodox manner. Detailed descriptions are given of the extent to which these methods can be used in the differential diagnosis of lesions of the central nervous system and its membranes.

A feature of the book is the large number of diagrams illustrating the mastic, gold, benzoin and other colloidal tests. The reviewer wishes he could share the obvious enthusiasm of the authors for these tests, and their interpretation of the 'minimally pathological curves'. One would also not expect 'Ayala's index' or the 'Boveri reaction' to be mentioned in a modern text-book.

This volume should serve as a stimulus for investigators who wish to probe more deeply into the significance of the cerebrospinal fluid.

A.A.K.

## CORRESPONDENCE : BRIEWERUBRIEK

### 'MEDICAL REPRESENTATIVES'

*To the Editor:* As a medical representative of 22 years' experience I should be grateful for the courtesy of your columns in which to comment on the situation mentioned by *Physician*[1] in the *Journal* of 1 September.

While much of what *Physician* says is true, I hope and believe that most medical practitioners do not share his indiscriminate dislike of all medical propagandists.

The present situation of 'over-saturation' has been brought about by an irresponsible sales policy on the part of some of the bigger drug-companies, who may be very sound in their other departments.

The more conservative sales organizations like to employ as medical representatives men with a good background of pharmacy, medicine, or some allied branch of science, and with a sound general education and a pleasant personality and tactful manner. They are subsequently thoroughly trained in basic anatomy, physiology, bacteriology, pharmacology and in all aspects of their company's products and their uses. Some companies sometimes even send their men overseas for special training courses. I for example spent 3 months in a hospital for a particular group of diseases, doing what was virtually a condensed postgraduate medical course. I also spent 2 months at the London School of Tropical Medicine for general experience. Whatever *Physician*

believes, I can assure him that a big majority of general practitioners and quite a number of specialists learn the finer points of usage or pharmacology of a particular product from such a medical representative more frequently than through the literature. The literature must of necessity always lag behind current knowledge of the product. No busy practitioner can read all the world's leading medical journals, but the major drug companies have the means to locate and abstract all references (favourable and unfavourable) to their products, and this information is immediately made known to the medical representative.

Companies favouring this type of representative normally employ from 5 to 8 such men in the Union, and they cannot visit a doctor much more frequently than once in 6-8 weeks.

Now we come to the delinquent companies who, although they are in a minority, are able to cause much ill-feeling on the part both of doctors, and of medical representatives with a sense of professional pride in their work and their mission. Unfortunately the doctor, like *Physician*, often fails to differentiate between the genuine article who can be of assistance to him, and the counterfeit who causes him trouble and is able to give little or nothing, except possibly a sample, in return. How does this counterfeit article get into circulation?

This minority of companies employing such men is following a deliberate policy of 'quantity not quality', and unleashes anything from 20-30 representatives per company on the medical profession of this country, with the result that doctors have to suffer their visits at intervals of about a week. It is not surprising that *Physician* and some others have come to consider all medical representatives something of a nuisance—since they see the nuisances some 6 times more often than the helpful ones. Companies following this policy do not require high educational standards of their employees, nor do they 'waste' time training them; their function is merely to get a foot in the doctor's consulting room, 'plug' the product name, and leave a pamphlet and an embarrassing supply of samples, seemingly in the hope that the unhappy practitioner will *have* to start using the material or else be crowded out of his own rooms by the bulk of free supplies! After all, the aim of all medical propaganda, whether conservative or high-pressure, is to get the doctor to *start* using the product. Once started, he is likely to continue if the product has merit.

What is the remedy for this situation? I submit to *Physician* that to ban all medical representatives is not only to punish the innocent with the guilty, but to deny himself a useful source of recent information on products mainly useful in his work.

Why not instruct all receptionists to keep a small register of representatives and black-list any who obviously waste the doctors' time. The employing company should be black-listed as well. This procedure should rapidly correct the current abuses, and make life happy again for both representative and doctor.

Regarding the heavy bombardment of doctors with mailed printed matter, I agree entirely and suggest that this should at once be reduced by voluntary agreement among the manufacturers, analogous to the Code of Advertising Standards agreed upon by the Newspaper Press Union. As a suggestion, each company might well be limited to, e.g., 4 mailings a year; none would suffer, since all would be on the same footing.

Where the plethora of drugs is concerned I find myself, for the first time, in disagreement with *Physician*. Surely it is not an evil trend, since the more new drugs developed the better: some will be discarded, some will survive unchanged and others will be modified or developed into something better, but without the enterprise that goes into research and production we should not now have soluble neutral aspirin, tetracycline, the lente-insulins and non-addictive antitussives, to mention just a few useful recent developments. That streptomycin, prontosil-rubrum and mandelic acid have not lived up to original expectations does not detract from the value to the medical profession of the initiative of the commercial research that produce them.

What is possibly objectionable to the doctor is duplication of the same products, under different names, by different makers; but is even this an evil? Without such various competitive sources of supply one would still be paying 20s. for 20,000 units of penicillin. If it is objectionable to the doctor he should remember the benefits conferred on the patients.

*Medrep*

6 September 1956

1. *Physician* (1956): S. Afr. Med. J., **30**, 852.

## 'MEDICAL REPRESENTATIVES'

*To the Editor:* Your correspondent[1] typifies the enormous contention that scientific advancement can be a function of independent and self-sufficient endeavours. Although the historical antecedents to any great discovery invariably reveal the cumulative achievements of many and diverse specialists, your correspondent sees fit to dispense with the invaluable services which are rendered by those persons who specialize in the clinical intricacies of ethical products.

The confusing and yet inevitable 'plethora of drugs now being released on the market' itself creates a need for an expert on these preparations to advise the physician accordingly.

The doctor cannot possibly cope with the demands of his everyday commitments and also find time to fully familiarize himself with the growing stream of medical discoveries. Merely to read journals and periodicals, as your correspondent suggests, is obviously insufficient. However, I am happy to be able to say that it has been my experience that the majority of medical men are well aware of the crucial and important services offered by medical representatives, and a very cordial welcome has always been extended to me at the doctors' consulting rooms.

In view of your correspondent's negative attitude, however, I shall be much obliged if you would furnish me with his name and address, so that I may avoid adding to his 'major problem'.

Ben Kessel

P.O. Box 1019
Johannesburg
5 September 1956

1. *Physician* (1956): S. Afr. Med. J., **30**, 852.

## THE RHESUS FACTOR IN DURBAN INDIANS

*To the Editor:* Two recent papers summarized the results of treatment of Rh-immunized mothers at the Addington Hospital Rhesus Clinic. Wallace *et al.*[1] reviewed all cases since the Clinic's inception, while Pretorius[2] reports 66 cases in the two year period from 1 August 1951 to 31 July 1953. The latter is not a separate series but is part of the larger one analyzed in the former report.

Unfortunately Pretorius makes one statement which I, as Director of the laboratory responsible for the serological tests not only of his cases, but of all ante-natal cases in the Natal region, cannot pass unchallenged. He says that 'all Indian women resident in Natal are virtually all Rhesus-positive'. This is not so, and although the Indian frequency of Rh-negative bloods is lower than the European it is still sufficiently high to make routine ante-natal testing worth while.

No blood group frequencies appear to have been published for Indians in Africa, but in India Mourant[3] quotes Rh-negative frequencies varying from 2% in Bombay to 10% in Calcutta with an apparent average of around 5%.

Amongst 1,330 Indian blood donors bled at least once by the Durban Blood Transfusion Service this year, the group frequencies were: O− 517 (38·87%); *A*− 284 (21·35%); *B*− 448 (33·69%); *AB*− 81 (6·09%); *Rh*-positive—1,269 (95·27%); *Rh*-negative (*cde*/*cde*, *Du* tested)—63 (4·73%). Although these figures are weighted with family material, they demonstrate the practical problem—there are over 14,000 Rh-negative Indians in Natal, about one-half of whom live in Durban. For this reason we consider ante-natal Rh-testing to be of value in the Indian community and to be a test which should be carried out routinely in ante-natal clinics.

The proof of the pudding is in the eating! In the *last two months* we have found 32 Rh-negative Indian women (26 in Durban) from routine clinic tests, and have had to transfuse 2 Indian babies with haemolytic disease.

John C. Thomas

Blood Group Reference Laboratory
Durban Blood Transfusion Service
1 September 1956

1. Wallace, H. L., Edge, W. B., Mann, N. M. and Moores, Phyllis (1956): S.A. Med. J., **30**, 681.
2. Pretorius, H. M. (1956): S. Afr. Med. J., **30**, 739.
3. Mourant, A. E. (1954): '*The Distribution of the Human Blood Groups*'. Blackwell Scientific Publ., Oxford.